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**JOURNAL OF  
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**THE MOUNT SINAI HOSPITAL OF NEW YORK**  
**POSTGRADUATE COURSES IN CLINICAL MEDICINE**

*given in affiliation with*  
**COLUMBIA UNIVERSITY**

**January 1st through May 25th, 1954**

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THE MOUNT SINAI  
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CONTENTS

OBITUARY.....	1
EDITORIAL.....	2
NEW ASPECTS OF PATHOGENESIS OF EXPERIMENTAL POLIOMYELITIS. <i>Gregory Shwartzman, M.D.</i> .....	3
PLASMA LIPID PARTITION OF THE NORMAL AND CHOLESTEROL-FED RABBIT. <i>Chun-I Wang, M.D., Louis E. Schaefer, M.D., Stanley R. Drachman, M.D. and David Adlersberg, M.D.</i> .....	19
INTERATRIAL CONDUCTION DEFECTS ASSOCIATED WITH SUPRA- VENTRICULAR TACHYCARDIA IN INDIVIDUALS WITHOUT ORGANIC HEART DISEASE. <i>M. B. Walters, M.D. and A. Grishman, M.D.</i> .....	26
NUMERICAL EVALUATION OF OCULAR SIGNS OF ESSENTIAL HYPER- TENSION. <i>Heury Minsky, M.D.</i> .....	29
PATHOLOGIC ANATOMY IN MODERN MEDICINE. <i>Paul Klempner, M.D.</i> .....	38
A REPORT ON THE USE OF THE STARCH SPONGE CONE IN PROSTA- TECTOMY. <i>Gordon D. Oppenheimer, M.D., Leonard Biel, M.D. and Edward J. Frishwasser, M.D.</i> .....	45

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SOLON S. BERNSTEIN, M.D.

*1896-1953*



## In Memoriam

SOLON S. BERNSTEIN

1896-1953

All who have known Solon Bernstein share a common heritage in the memory of a rare person. Those of us who had the privilege of knowing him well may say with deep truth that they are the better human beings for having known him. We who shared with him the joy of work's accomplishment in the Hospital saw constant examples of his paternal kindness, his inexhaustible patience, his trained understanding and the warm sympathy which made him the true physician. As a scientist he hungered for knowledge, unhappy in the vast ignorance which still shrouds so many of our medical problems. He read widely, he studied, he worked to learn whatever he could use for the benefit of the sick.

We, his colleagues, respected him for his modesty, his sincerity, his intellectual integrity. We admired him for his ability, the unusually wide range of his interests and his precise and beautiful English, written and spoken. We loved him for his dependability, for his cordiality, his graciousness and that ever-ready sense of humor which was never vicious, never caustic and never belittled anybody. He would use it to point an argument; it often lightened a moment of tension or fatigue. Nurses, Interns always admired him for his patience, his knowledge and willingness to teach.

He inspired his friends by the way he strove constantly to overcome his shortcomings. No one could have imagined the diffidence, the uncertainty and the deep insecurity which plagued him for years. No one could have guessed that who saw his efficient, apparently effortless accomplishments. That urge for self-improvement gave him his deep interest in literature, history, music. His pervading love for mankind brought him adoring patients and devoted friends, and motivated his eagerness to serve his fellow human beings.

His friends are grateful that he lived so full a life — in various ways a very full life. He had such a variety of interests, so wide a knowledge of them, so discerning a vision of world affairs and of people that he may well be likened to “the swan which soars aloft and surveys the world, leaving the earth-bound peacocks to strut and boast.”

DAVID BECK, M.D.  
for the EDITORIAL BOARD.

## EDITORIAL

Twenty years ago the late Joseph Globus wrote the opening editorial for the Journal of the Mount Sinai Hospital, setting it in the path it followed until his death two years ago. The brief tenure of Solon Bernstein interrupted by his illness and terminated so abruptly by his untimely death saw no change in these policies.

It is now the duty of the new Editor and the Editorial Board to re-examine the purposes of the Journal, and either to reaffirm the old aims or fix new ones.

We believe that a major aim of the Journal, now as then, is to make available its pages for case reports based upon the extraordinary clinical material which our Hospital has always had, some of which might otherwise be lost. Close observation, accurate, concise description, and detailed reporting are to be encouraged. We hope to foster the type of medical writings exemplified so brilliantly by men like Parkes Weber, and our own great Emanuel Libman. The Journal would prefer these papers to come from the ranks of the House and Resident Staffs, Fellows, and younger men generally. We are therefore offering an annual prize to be known as the Joseph H. Globus Memorial Prize for the best such paper published in the Journal during each calendar year. The prize may not be won by anyone of Associate or Attending rank and is open to all other Mount Sinai Hospital workers. The subject may pertain to any clinical aspect of medicine, surgery, or the other specialties, based upon material from the Mount Sinai Hospital.

At the other end of the spectrum we hope to publish from time to time fruits of the maturity, wisdom and experience of our Nestors, our Elder Statesmen, men who through their own medical lives and those of their teachers have encompassed all the rise of modern medicine—men who have themselves made and in most instances are continuing to make many of the contributions which have made our Hospital great. From them we hope for philosophy, for perspective, for prophecy, for new directional signposts, for approbation and admonition.

From the active workers of established position we desire no more than a tithe of their productivity.

The clinico-pathological conferences and the monthly conferences are rich mines ripe for exploitation, the many named lectures will continue to be reported whenever possible. Brief general reviews of newer expanding experimental fields by men who are making their own contributions within them will be welcomed.

Finally, we hope that the Journal will be representative of all the Hospital and every department, and that every worker, clinical or laboratory, will support it, read it, and write for it.

## NEW ASPECTS OF PATHOGENESIS OF EXPERIMENTAL POLIOMYELITIS<sup>1, 2</sup>

GREGORY SHWARTZMAN, M.D.<sup>3</sup>

*New York, N. Y.*

Dr. Schick, Dr. Hodes, ladies and gentlemen. It is indeed a great pleasure and honor to give a Bela Schick Lecture, for two reasons: my respect for Dr. Schick's important scientific achievements and personal feeling of profound friendship. The beginning of our personal relationship dates back many years. I remember well our first meeting a little over thirty years ago, at a dinner on the roof of a midtown hotel, shortly after Dr. Schick was invited to take charge of the Department of Pediatrics. A few years later I joined the Hospital and from that time on I profited greatly from his stimulating friendship. But I am only one of his many, many admirers. To bear witness is the fact that eleven years ago, when Dr. Schick was about to retire from active hospital service, his successor to be, and his associates and assistants got together to found this lectureship in his honor.

The subject of my lecture is an old story which always remains new. I don't think it will be an exaggeration to state that there is no disease which has proved more provoking to the imagination of investigators than poliomyelitis. Indeed there are many puzzling features of the disease which have been studied and vividly discussed in thousands of papers published since 1909, when Landsteiner and Popper initiated all experimental work by transmitting the disease from man to monkey.

It is my intention to deal tonight with the pathogenesis of the disease in the light of our investigations carried out during the past few years.

Before proceeding, I wish to acknowledge my deep indebtedness to the National Foundation for Infantile Paralysis, whose generous support made these studies possible, and to my research associates, men of outstanding ability, skill and great enthusiasm, namely, Drs. Stanley Aronson, Max Adler and Constantine Teodoru, whose active participation has been essential in carrying out these investigations.

Research on the pathogenesis of poliomyelitis went through various cycles which are well known and need be mentioned only very briefly. For many years the virus was considered to be strictly neurotropic on the basis of demonstration of the propagation of the virus in the monkey from the olfactory mucosa to olfactory bulbs and down the brain stem to the spinal cord, and other numerous experiments which need not be described here. The idea that the nasal mucosa serves as a portal of entry in the natural disease was soon abandoned for lack of

From the Department of Microbiology, The Mount Sinai Hospital, New York, N. Y.

<sup>1</sup> Bela Schick Lecture delivered November 6, 1953 at The Mount Sinai Hospital, New York, N. Y.

<sup>2</sup> Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

<sup>3</sup> Director, Department of Microbiology, The Mount Sinai Hospital, New York, and Professor of Microbiology, Faculty of Medicine, Columbia University.

specific lesions along this pathway, in view of the finding of the virus in the stool of patients in the course of the disease, and also due to the fact that the disease could be produced in monkeys by the feeding of the virus. Up to recently, a number of facts placed the disease in a category of its own, pointing to essential differences between the pathogenesis of poliomyelitis and other neurotropic viruses. In contrast to other neurotropic diseases, the poliomyelitis virus was only rarely isolated from the blood. It was shown to propagate along the peripheral nerves following direct inoculation. Very recently, however, Bodian and Horstmann demonstrated clearly a viremia in orally infected chimpanzees and human contacts, making necessary reconsideration of the pathogenesis. Bodian now postulates the existence of three phases in the pathogenesis, namely, alimentary, vascular, and neural. The existence of a vascular phase preceding the neural one is of theoretical and practical importance. It allies the disease to other neurotropic diseases and suggests that there is a period of grace during which it may be possible to prevent the entry of the virus into the nerve tissues by immune or chemotherapeutic agents.

In addition to the mode of progression of the virus, another aspect even more puzzling should be considered under the heading of pathogenesis, namely, variations in predisposition to the experimental and natural disease, depending on a variety of non-specific factors unrelated to presence or lack of specific immune reactions. These factors are most conspicuous in relation to the incidence of paralysis in one out of one hundred to one out of one thousand of those actually infected with the virus. Only to mention a few, namely, over exertion, drastic changes in temperature (chilling or heat), surgical trauma, infections, immunization with vaccines and toxoids and the like. Pregnancy appeared to me one of the most interesting known factors of predisposition to poliomyelitis<sup>4</sup>. Indeed, if an endocrinological disturbance were found to be responsible for the enhancement of the disease, a common denominator could be found for seemingly unrelated factors just mentioned.

Since it was shown by Venning that during pregnancy there occurs a greatly increased excretion of corticosteroids, an experiment was devised by me three years ago to determine the effect of cortisone upon experimental poliomyelitis. Because enhancement of the disease was sought, the selection of a partially refractory animal proved of paramount importance. In the course of some other work, I became familiar with low incidence of paralysis and low mortality rate following inoculation of high concentrations of poliomyelitis virus into the Syrian hamster. The effect of cortisone upon poliomyelitis infection in this animal proved indeed dramatic. The animals pretreated with cortisone died from a violent, widely disseminated disease within a few days following inoculation of the virus. Since then numerous studies have been carried out by us in various directions.

Tonight I shall review the information obtained through this approach relative to the aspects of pathogenesis reviewed earlier.

<sup>4</sup> It is of interest in this connection that in 1939 Hodes found that pregnancy interferes with development of acquired immunity and diminishes a previously established immunity in mice to St. Louis encephalitis.



TABLE I

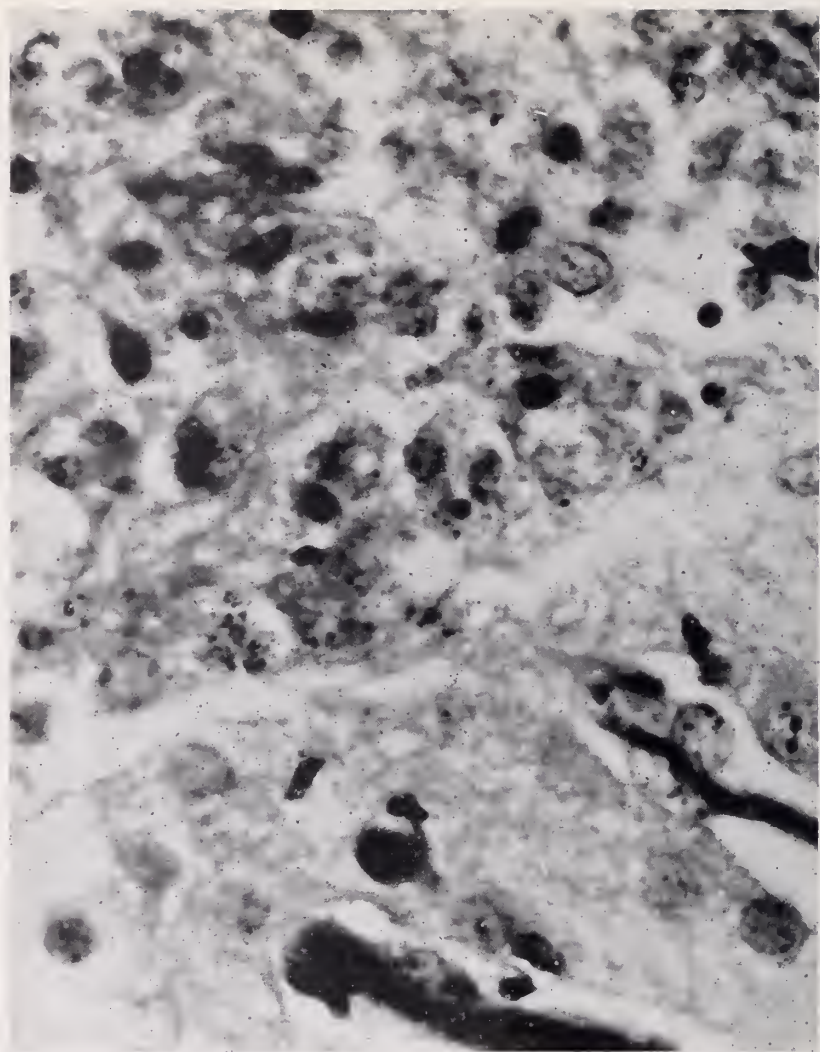
*Cortisone enhancement of experimental poliomyelitis in the Syrian hamster*

ROUTE	WITHOUT CORTISONE		WITH CORTISONE	
	Paralysis	Mortality	Paralysis	Mortality
Intracerebral . . . . .	45%	24.4%	100%	100%
Intraperitoneal . . . . .	0	0	100%	100%
Intramuscular . . . . .	0	0	100%	100%
Subcutaneous . . . . .	0	0	100%	100%

Following the demonstration of great enhancement of the disease with cortisone following intracerebral infection, it was soon found that the hamster becomes equally highly susceptible to infection by peripheral routes as shown in Table I.

These experiments were then followed by a long series of studies on the histopathogenesis of the disease and on the progression of the virus from the sites of inoculation.

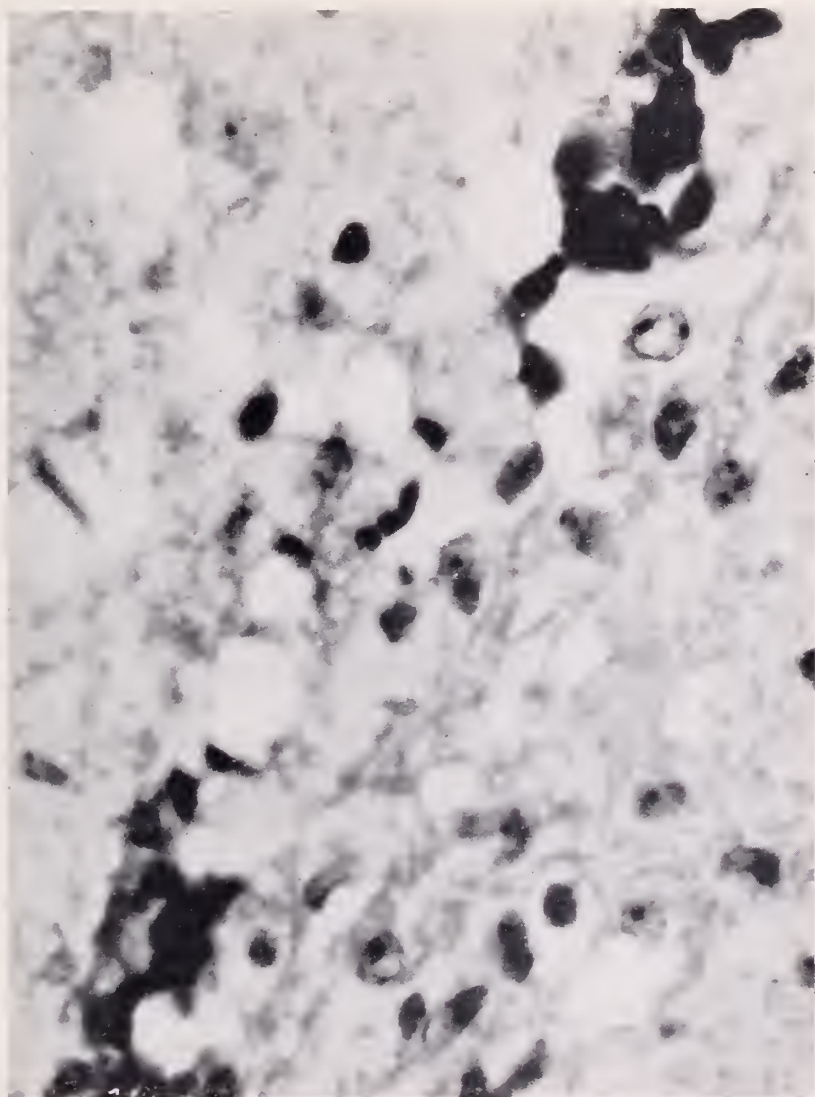
In the normal hamster, four days following an intracerebral inoculation of MEF<sub>1</sub>, typical lesions are confined to the midcerebral parenchyma in the vicinity of the inoculation depot (i.e., neocortex, hippocampal cortex and septum regions). Such lesions are characterized by exuberant interstitial and perivascular inflammatory response. Cortisone-treated hamsters, inoculated similarly and sacrificed at four days, show in contrast, a greater spread of lesions (i.e., olfactory cortex, neocortex, hippocampal cortex, and cervical cord involvement), a tendency toward bilaterality of lesions and a perceptibly inhibited inflammatory reaction. In the normal hamster, seven days following intracerebral inoculation of MEF<sub>1</sub>, typical lesions are demonstrable in patchy, isolated areas caudal to the site of inoculation; some spinal cord anterior horns are implicated, but most show no evidence of infection. In contrast, cortisone-treated MEF<sub>1</sub> inoculated hamsters sacrificed after seven days, display a pattern of widespread, bilateral neuronal necrobiosis both caudal and rostral to the inoculation depot, all levels of the spinal cord being involved. Suppression of inflammatory reaction is again apparent, but not as pronounced as in previous days. The striking differences in histological manifestation in cortisone-treated and untreated animals are illustrated in microphotographs 1-5. Thus, cortisone enables the virus to disseminate contralaterally and also permits a retrograde ascendancy. Untreated hamsters fail to show a retrograde progression. In simian poliomyelitis, olfactory bulb involvement is not usually seen unless the olfactory nerve receptors are exposed to the virus. In our studies on cortisone-treated monkeys, typical lesions could be found in the olfactory bulb irrespective of the portal of viral entry. It is noteworthy, however, that no ubiquity of central nervous system lesions is found under the influence of cortisone. Only neural sites potentially susceptible to the virus are affected. The problem of retrograde ascendancy in cortisone-treated animals remains to be solved. It is possible that increased concentration of virus under the influence of cortisone is responsible for retrograde intraneural dissemination. The other possibility is that the presence of a pronounced viremia, to be dis-



MICROPHOTOGRAPH 1. Intracerebral needle tract, in hamster, after 4 days; note extensive cellular reaction and microglial response. H. & E.  $\times 190$

cussed later, allows the establishment of widely disseminated lesions in all susceptible sites by way of the vascular system.

An interesting point emerges from these studies in reference to histopathogenesis of the disease. In the past the question has been raised whether the mesodermal inflammatory reaction, typical of poliomyelitis, namely, leucocytic, microglial and endothelial responses are of primary or secondary nature; whether the virus directly incites these changes or whether the essential activity is neuronal necrosis with the inflammation evoked by the products of necrobiosis. Howe and Bodian who injected poliomyelitis virus into an area devoid of neurons found that the virus produced no effect upon the glial cells but travelled inconspicu-

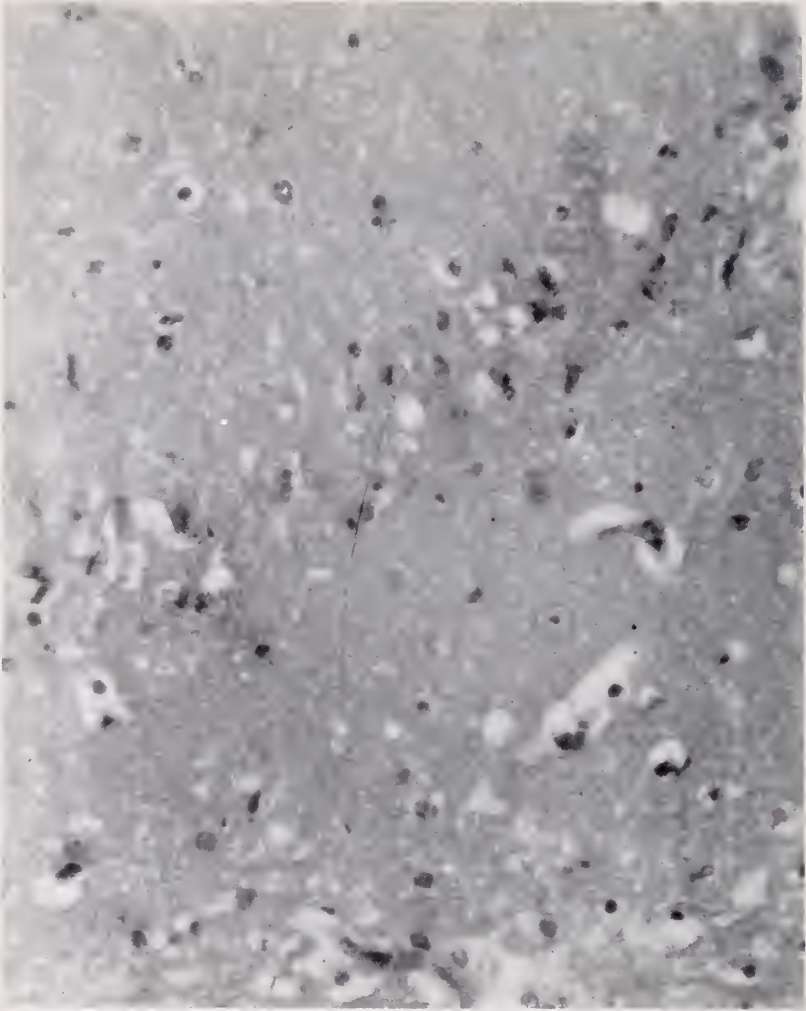


MICROPHOTOGRAPH 2. Intracerebral needle tract, in cortisone-treated hamster, after 4 days; resolution of hemorrhage and poor cellular reaction. H. & E.  $\times 190$

ously to areas rich in neurons. Rivers concluded that degenerative changes are a primary effect of viruses, with inflammation being secondary in nature. Experiments with cortisone which are capable of dissociating the effects of viruses from those of the host by hindering reactive processes, bring ample proof to the contention that the primary effect of poliomyelitis virus lies in the neuronal damage.

In addition to central nervous system lesions, there were also noted in cortisone-treated hamsters infected with the virus, severe myositis and necrosis of so called "brown fat" (microphotographs 6 and 7). Although also present following





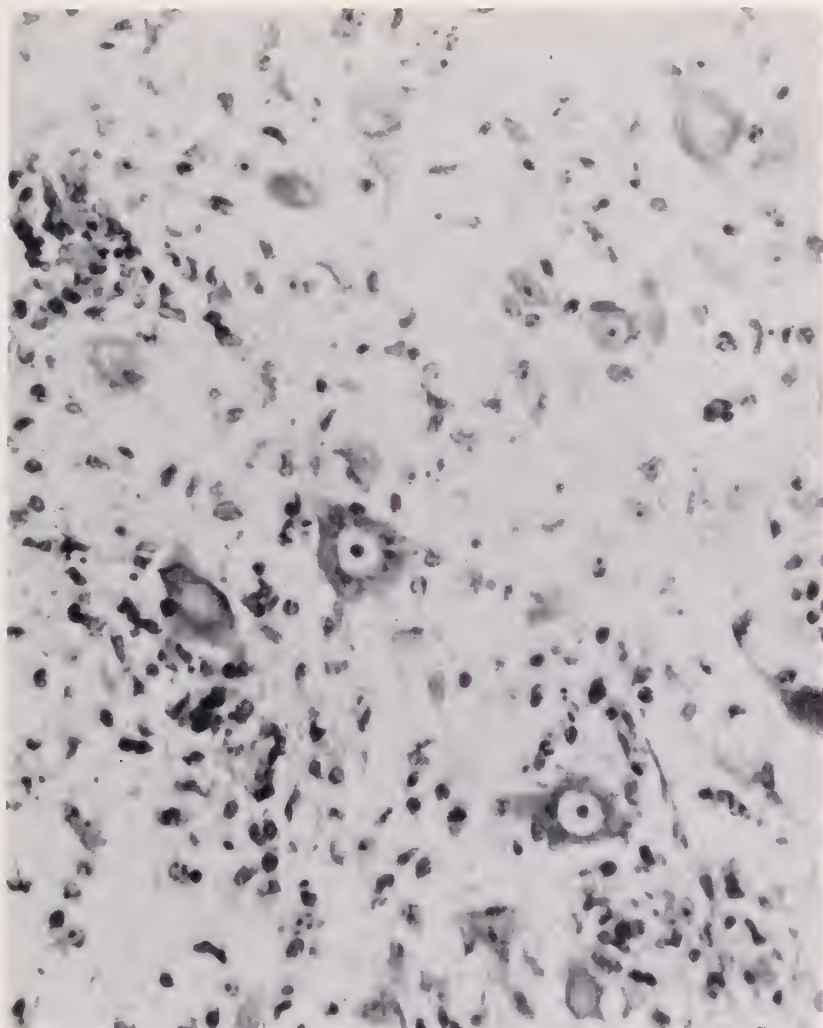
MICROPHOTOGRAPH 3. Hippocampal cortex in cortisone-treated hamster, sacrificed 7 days after intracerebral inoculation of MEF<sub>1</sub>. Diagonal line represents former site of cortical neurons. Negligible inflammatory or vascular response. H. & E.  $\times 70$

intracerebral inoculation, they were especially conspicuous following peripheral-inoculation of the virus. These lesions failed to appear in infected hamsters receiving no cortisone.

Since two factors (cortisone and virus) were introduced into the animal, the specificity of the lesion remained to be proven. These control hamsters were injected with cortisone and normal mouse brain emulsion and sacrificed at various time intervals. In several hundred controls 3 hamsters showed comparable lesions, bearing, however, no relation to the site of cortisone or brain emulsion inoculation. This result was interpreted as due to activation of some latent virus.

The histology of the myositis is remarkably similar to that produced by Cox-

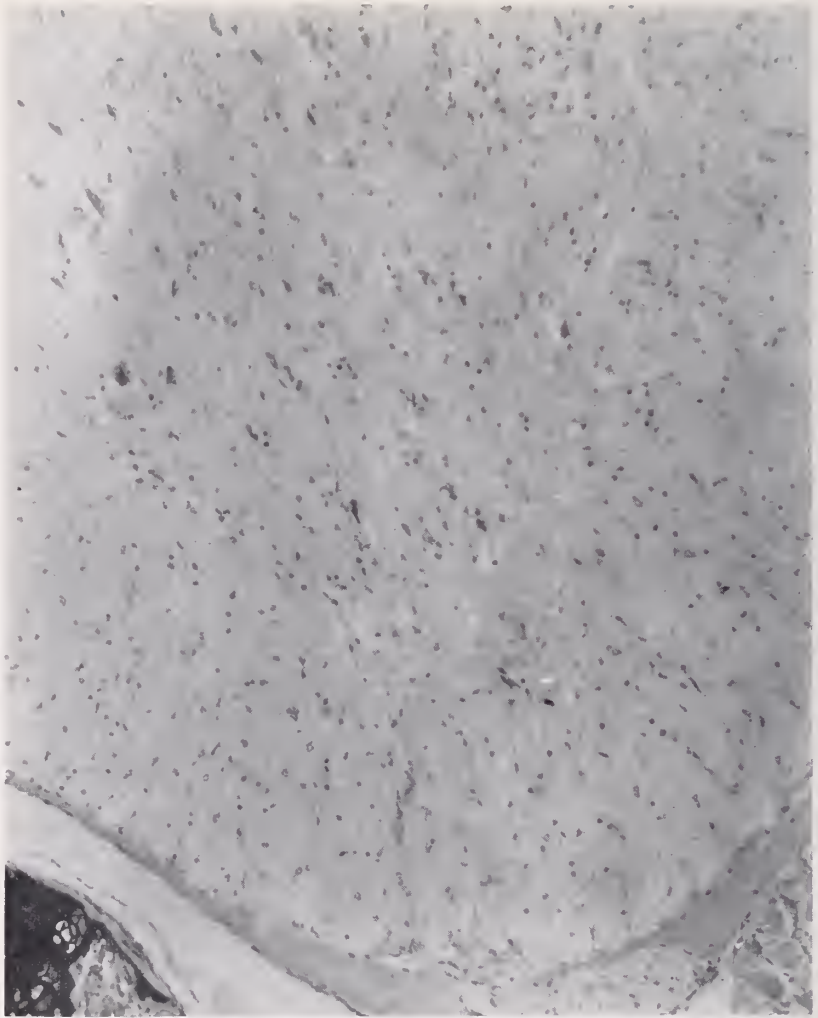




MICROPHOTOGRAPH 4. Spinal cord in untreated hamster sacrificed 7 days after intracerebral inoculation of MEF<sub>1</sub>. Moderate neuronal loss; widespread inflammatory reaction. Thionine.  $\times 190$

sackie virus. This statement should not be interpreted, however, as a claim of a relation between poliomyelitis and Coxsackie viruses, since murine viruses are also capable of producing myositis. It became necessary, however, to prove that our poliomyelitis virus was free of murine and Coxsackie viruses which we did in a series of control studies such as neutralization studies and failure of our virus to produce any lesions in suckling or adult mice or in hamsters receiving no cortisone.

The strict localization of the lesion in the brown fat should be borne in mind in connection with the work to be described later. The above studies on the histopathogenesis were accompanied by experiments designed to determine the pro-



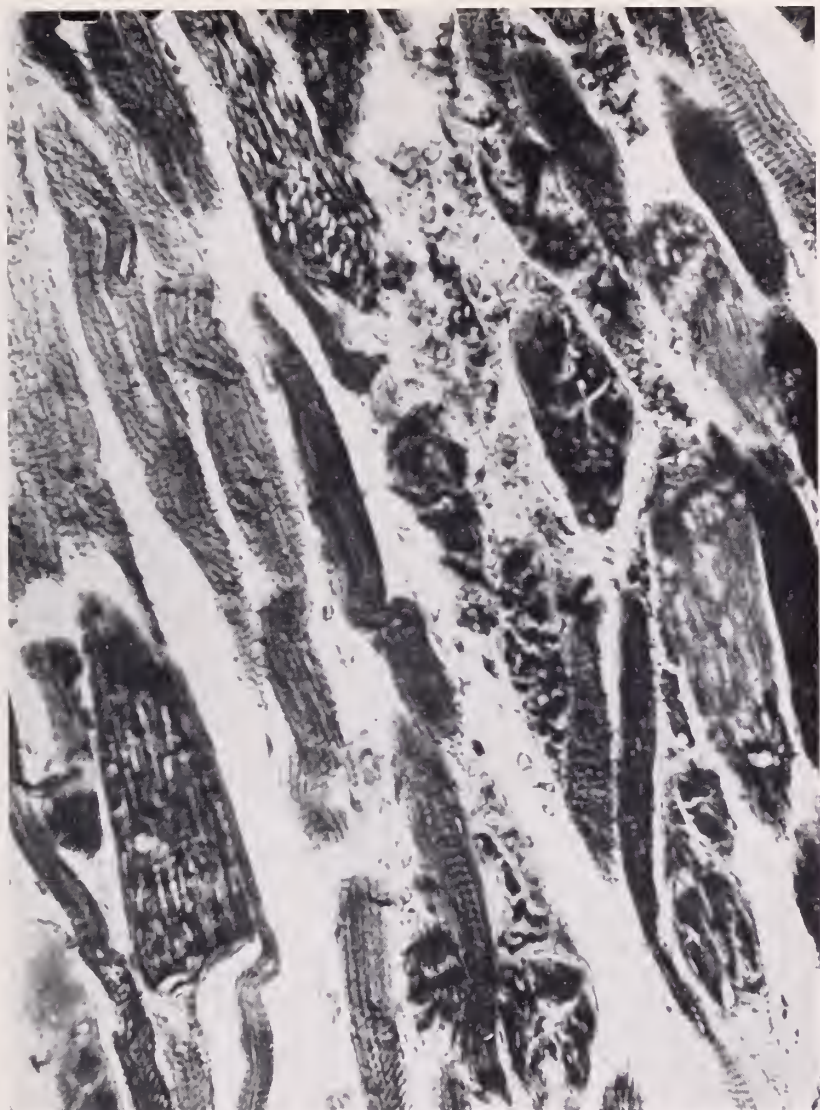
MICROPHOTOGRAPH 5. Spinal cord in cortisone-treated hamster sacrificed 7 days after intracerebral inoculation of MEF<sub>1</sub>. Total loss of anterior horn ganglion cells with paucity of cellular reaction. Thionine.  $\times 70$

gression of the virus from peripheral sites of inoculation, namely, intraperitoneal, intramuscular and subcutaneous routes. Many different tissues were removed from the hamsters and tested for viral concentration in mice. It is from this drawn out and tedious series of experiments that we obtained rather intriguing results.

A number of viscera, including white fat, failed to show any virus at any time.

Within a few hours following intraperitoneal inoculation, the virus disappeared from the peritoneal cavity and regional lymph nodes. It appeared, however, after active multiplication in other tissues, namely, in periadrenal fat and paravertebral muscles, (Figure 1 and Table II).

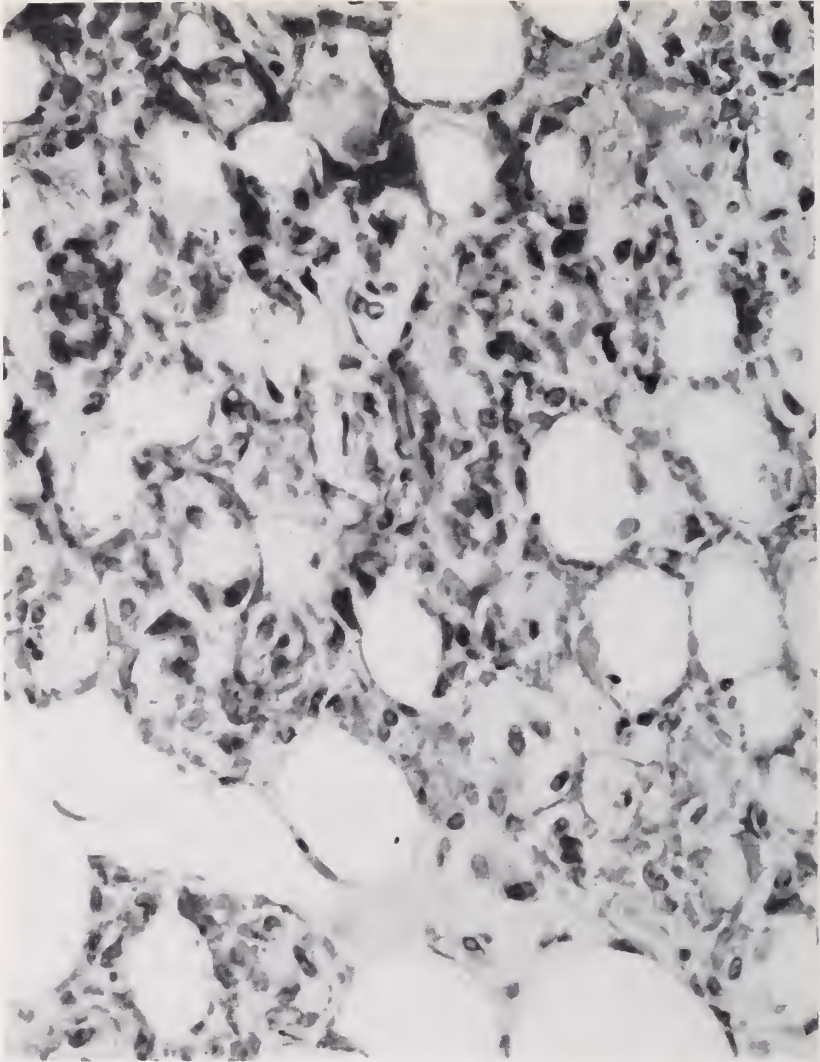
At first we were critical about these results, considering the possibility that the



MICROPHOTOGRAPH 6. Advanced viral myositis in cortisone-treated hamster; note irregular loss of striations, hyaline degeneration, and cell necrosis; inflammatory reaction minimal. Phosphotungstic acid-Hematoxylin.  $\times 100$ .

virus injected was merely mechanically trapped and concentrated in this site following intraperitoneal inoculation or was caused by the incidental viremia. However, against this assumption, we had the observation that bloody organs, such as spleen and liver, were devoid of virus, and that the course of viremia bore no relation to the concentration of the virus in the fat (Table II). This selective extraneural localization was proven, however, beyond doubt in subsequent experiments in which the front left leg muscle of cortisone-treated hamsters were





MICROPHOTOGRAPH 7. Far advanced necrosis within brown fat in cortisone-treated hamster; foci of calcification present as well as early granulomatous reaction. H. & E.  $\times 190$ .

injected with the virus intramuscularly or subcutaneously and various tissues were titrated for viral concentration in mice, (Figures 2 and 3, Table III).

Invariably, irrespective of the site of inoculation, the brown fat showed very high titers at the early stages of the disease, a mere elution with water being sufficient to yield titers as high as  $10^{-6.2}$ .

Since the fat has a rich nerve supply, it was important to determine whether the nerves were responsible for the multiplication of the virus in this tissue. The interscapular brown body was removed surgically from its bed, thus severing all nerves and vessels. It was returned to its natural site and surgical closure was

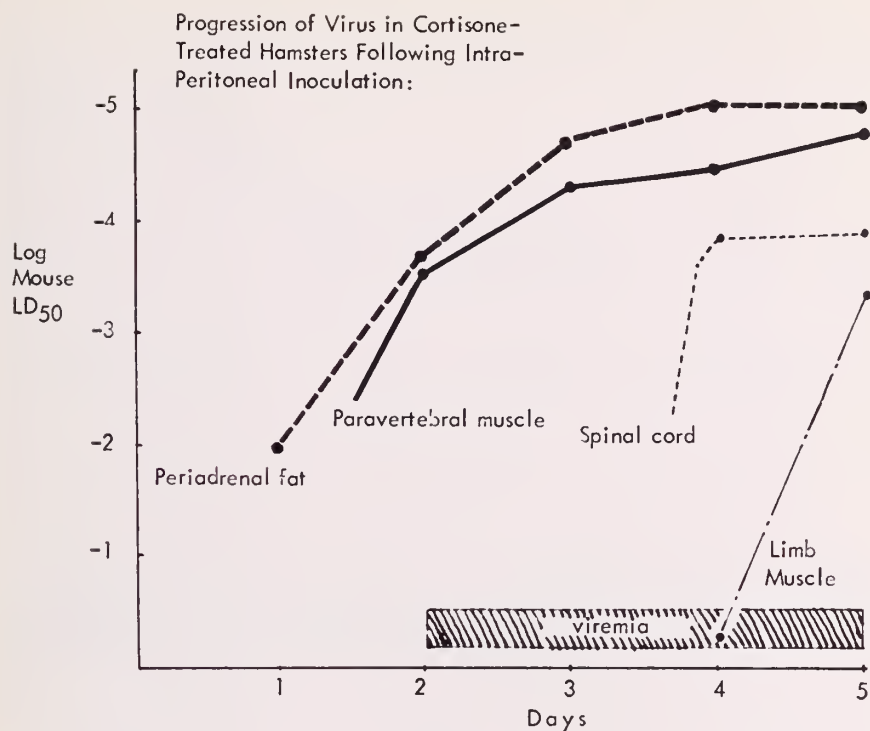


FIG. 1

TABLE II

*Viremia following intraperitoneal inoculation of virus into cortisone-treated hamsters*

HOURS	LOG OF LD <sub>50</sub> *			
24	0	0	0	0
48	>3.0	3.0	2.7	>3.0
72	>3.3	3.0	3.3	>3.0
96	>3.3	0	3.0	2.8
120	1.7	0	0	3.0

\* Each figure represents LD<sub>50</sub> of virus in the blood of one hamster, as determined in mice.

performed. Four days after the operation, the blood supply was completely re-established to the amputated fat. However, there was no regrowth of the nerves. Animals thus operated were treated with cortisone and were injected with the virus into the left fore limb. Three days later, the brown fat, as assayed in mice, showed a concentration of virus LD<sub>50</sub>10<sup>-5</sup>.

Later, I shall have occasion to dwell more on this rather unexpected tropism of the virus for a special type of extraneural tissue in connection with studies relative to endocrinological experiments. For the time being, I would like to say that the conspicuous modification, with the aid of cortisone, of the pattern of the

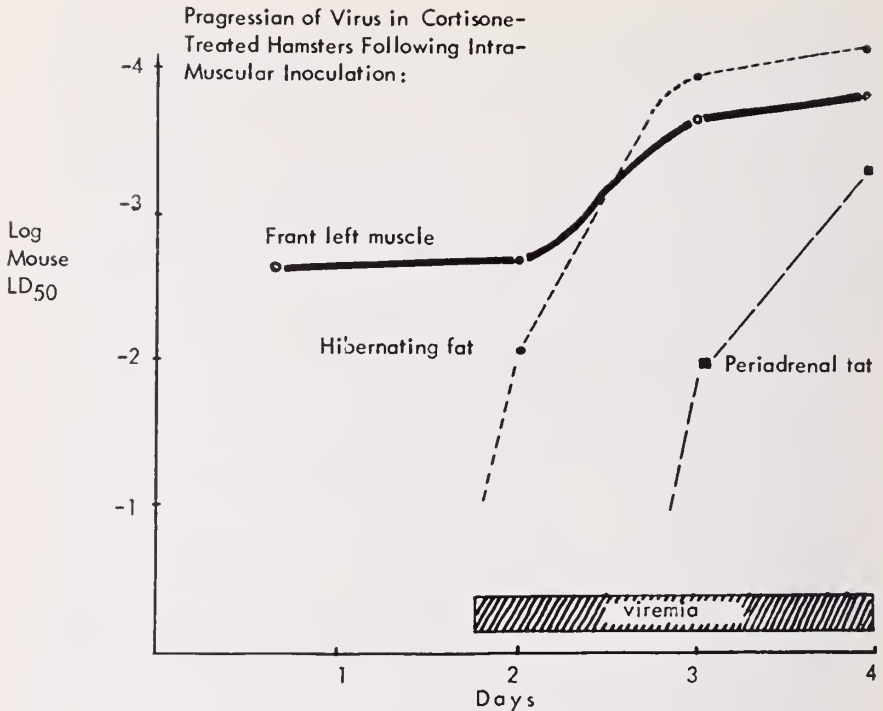


FIG. 2

disease seen in the hamster is also observed with other animal species. In the monkey, the expansion of the disease with the help of cortisone can be demonstrated in various ways:

The Brunhilde strain, which ordinarily gives a very low incidence of takes by the intramuscular route, may produce a prostrating rapidly progressing paralysis of the Landry type following inoculation by this route. In the hands of Sabin and our own, non-paralytic strains produced a paralytic disease in cortisone-treated monkeys. According to Bodian, and later confirmed by us, treatment of cortisone produces a high incidence of paralysis following intravenous inoculation of the virus.

In adult mice there occurs an acceleration of the disease under the influence of cortisone. The effect upon mortality is difficult to evaluate in view of a natural high susceptibility of mice to the infection. The effect of cortisone upon this species, however, can be demonstrated clearly in a two-fold manner. Untreated adult mice are totally refractory to the infection by the intraperitoneal route. Treatment with cortisone makes it possible to produce it by this route. Nevertheless, it should be stated that the results are not as uniform as in hamsters. The second method of demonstration is in the suckling mouse. The new-born mouse is significantly more resistant to the infection than the adult mouse. According to Sabin, the susceptibility is enhanced to the level of the adult mouse when cortisone is used. Now, what happens in other animal species which are totally refrac-

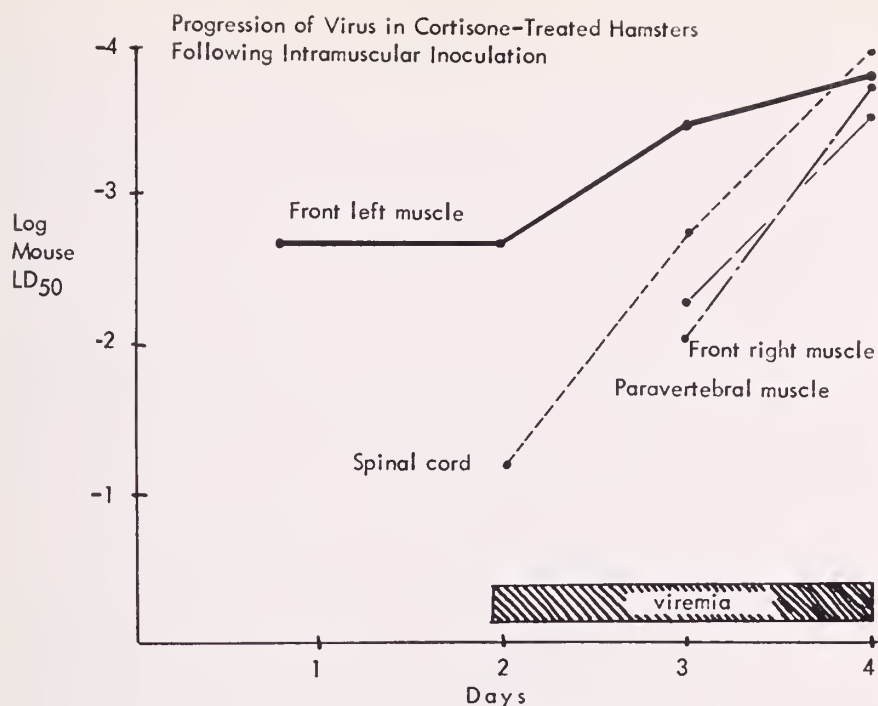


FIG. 3

tory to the infection? In our hands, no infection could be produced following most vigorous treatment with cortisone in rabbits, guinea pigs, albino rats, and Chinese hamsters.

Before proceeding any further it may be timely to attempt to interpret some of the results described in reference to pathogenesis of the natural disease.

In criticism, one may say that cortisone changes the behavior of the host so dramatically that the results are of little significance relative to the natural disease. In replying to this criticism, one can state simply that no matter how powerful the effect of cortisone may be the hormone cannot "make something out of nothing," namely, in no instance can the hormone make possible a viral infection in a totally refractory host. No matter to what degree the disease pattern may be expanded or altered, an inherent ability of the viral agent to establish an infection in the host must exist before the hormone can produce its augmentation. It is quite certain that the hormone is incapable of imparting new properties upon the virus itself. It is by making the host extremely sensitive, that the hormone becomes capable of exaggerating the events to such a degree that those of short duration and obscured by defense processes under natural conditions are brought into sharp relief for our study. It was shown clearly by Bodian that the previous failures to demonstrate a viremia in man and monkeys were due to an early appearance of antibodies in the blood. In our experiments, the removal of defense processes with the aid of cortisone, brings out a prolonged

TABLE III

*Progression of virus in cortisone-treated hamsters following intra-muscular inoculation*

HOURS	LOG OF LD <sub>50</sub>						
	Front Left Muscle	Front Right Muscle	Paravert. Muscle	Hibern. Fat	Peri-adr. Fat	Spinal Cord	Whole Blood
18	2.7	0	0	0	0	0	0
48	2.7	0	0	2	0	1.3	1
72	>3.6	2	2.3	3.9	2.7	2.7	2.7
96	3.8	3.8	3.3	4.1	3.3	3.9	2.6

viremia following intracerebral and peripheral inoculation of the virus. If the data are considered in this light, namely, that no new property is created in the virus itself, the value of the observation lies in the demonstration that the pathogenesis is not as unique and not as different from other neurotropic viruses as usually thought, (e.g., viral encephalitides).

The second part of our investigations deals with other endocrinological aspects of susceptibility and resistance to experimental poliomyelitis.

In the initial experiment it was noted that ACTH failed to produce the enhancement of infection obtainable with cortisone. In addition to cortisone, ACTH stimulates the production of other hormones as well. The possibility, therefore, remained that there may exist some hormones capable of reversing the enhancing action of cortisone. A series of endocrinological studies were initiated about the same time the observations were made on the lipotropism of the virus. The purpose of the following presentation will be to indicate some possible relationships of the brown fat to other endocrine functions and point out some correlations with susceptibility and resistance to the poliomyelitis infection in the hamster.

The brown fat also is designated in the literature as glandular, embryonal, alveolar and hibernating. The latter designation comes from the fact that in one location, between the scapulae, this fat is found in comparatively larger amounts in certain hibernating animals. This fat was recognized for many years as a distinctive form of lipid-containing adipose tissue, as opposed to white fat and found in all mammalian species, including man.

Several principal zones of brown fat are recognized, namely, in the interscapular region with extension into dorsal, cervical and axillary musculature; the thoracic region about the thymus and along the aorta, the abdominal region enclosing adrenal glands and about the renal vessels and inguinal region in the form of isolated depots. We have studied carefully the anatomic distribution of this fat in the hamster.

Histologically, the cells are smaller than white fat cells, they are round or polygonal with central nuclei, the protoplasm contains eosinophilic material and vacuoles containing lipids. The cells resemble other lipid storing endocrine glands.

Biochemical and histochemical studies indicate the presence of a great variety of substances in these cells, namely, phospholipid, glucolipid, alpha-amino acid groups, polysaccharides (water soluble), cytochrome oxidase, amine oxidase,



ascorbic acid, carbonyl groups, plasmalogens, alkaline phosphatase, succinic dehydrogenase, and esterase. We were able to confirm in our laboratory the presence of a number of these substances.

According to the literature, the discharge of lipids from the brown fat parallels the discharge of sudanophilic material from the adrenal cortex. Adrenalectomy and hypophysectomy deplete the brown fat lipids, while ACTH in the hypophysectomized animal prevents the depletion. In our own experiments the following relationships were noted. In a great number of experiments we attempted to establish the relation of growth curves of brown and white fat as related to the age of the animal best measured by its weight. No white fat can be found in the hamster fetus. The amount of brown fat is minimal. From the time of birth the amount of white fat increases precipitously and out of proportion to the increase in body weight, leveling off only after full maturity of the hamster. The amount of brown fat in the post natal hamster also increases. At an age corresponding to a body weight of about 20 gms., the accelerated growth ceases and the relative amount of brown fat in the body is maintained or diminished slightly through sexual development and maturity.

In view of the marked affinity of the virus for brown fat in cortisone-treated hamsters it was pertinent to determine the effect of this hormone upon the fat in the absence of viral infection.

Injection of cortisone parenterally results in a rapid and dramatic hypertrophy of brown fat masses, reaching after 7 days, a maximum of two or three-fold increase of brown fat volume and weight. This cortisone responsiveness is more apparent in the young, presexual hamster. As the hamster grows older, the response of brown fat to cortisone progressively diminishes. In removed tissues a relative reduction in water content was demonstrated, suggesting strongly that the hypertrophy was due to an increase in lipid contents of the cells. In parallel experiments it was also found that the ability of cortisone to enhance the poliomyelitic infection decreased with the age of the animal. The older the animal, the lower was the incidence of paralysis and mortality following the intracerebral inoculation of the virus. Furthermore, the percentage of takes by peripheral routes also decreased significantly in cortisone-treated hamsters of older age groups. Incidentally, it was noted that the response of the brown fat to cortisone also decreased with age.

Thus, there is strongly suggestive evidence that the changes observed in the brown fat are related to its susceptibility to virus infection.

Besides being related to cortisone and age, the weight of brown fat is also subject to seasonal variations, roughly paralleling seasonal changes in adrenal size and mirror-imaging the seasonal pattern of fluctuation in testicular size. Refrigeration at 5°C induces a moderate decrease in the weight of the brown fat beyond the fourth day, with an incidental decrease in the total dry residue and lipid fraction. It should be noted that there occurs also, in the refrigerated animal, a marked testicular hypertrophy, while cortisone leads to reverse. Consistently, castration brings about an increase in the amount of brown fat, treatment with gonadotrophic hormone resulting in the hypertrophy of this tissue.

Now we have arrived at some sort of a definition of the brown fat. It is an extremely reactive tissue closely linked up with a number of physiological functions. It is possible that the tissue may be endowed with some special endocrinological function, or that by virtue of its ability to act as a store house for physiologically important substances it reflects certain intricate activities of the body related to environment, temperature, stress, adrenocortical and testicular activity. It also happens that, in some instances at least, the variations in the tissue parallel susceptibility to experimental poliomyelitis infection in the hamster, the hyperactivity of the tissue coinciding with a remarkable affinity for the virus. Our preliminary experiments suggest that certain other endocrinological factors, castration in particular, which are capable of modifying the response of this tissue can increase to greater or lesser degree the resistance to poliomyelitis infection.

To sum up, many facts have been presented tonight which are intended to show that adrenocortical function and related activities of the body influence, in a rather intricate fashion, the predisposition to experimental poliomyelitis. The effects may be indirect. The modifications in the disease pattern may occur through alteration of certain defense mechanisms and by inducing alterations in some tissues, the brown fat in particular, which in turn permit the establishment of extraneural foci of larger quantities of virus than permissible under normal conditions. It appears, that under normal conditions of balanced endocrine function, the virus has to remain highly selective in view of the limited pathways which it is capable of utilizing and in view of the imposed restrictions upon the rate of multiplication. Conversely, a change in the endocrine balance of the host, directly or indirectly, opens new avenues of entry and affords new opportunities for rapid multiplication and, hence, a greater opportunity for a more general assault; thus converting the disease from a seemingly neurotropic to a pantropic disease. It is certainly not our intention to imply that the factors described are the sole agents responsible for susceptibility or resistance to the disease. We are certain, however, that they are important in determining the pattern of the disease.

It also happens that some of the factors of significance in the pathogenesis of the experimental disease also have been long recognized to be of lesser or greater importance in the natural disease, namely, various forms of stress, environmental conditions, seasonal variations, pregnancy, certain phases of menstrual cycle and others. Many of these factors are known now to have a common denominator, namely, their transitory effect upon endocrine function.

Obviously, there still remains much to be done to prove that we have found in our mode of attack upon the problem, a true pattern for the natural disease.

## PLASMA LIPID PARTITION OF THE NORMAL AND CHOLESTEROL-FED RABBIT<sup>1, 2</sup>

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Atherosclerosis is the most important degenerative disease of man. Although this condition can be produced experimentally in many species, e.g., the dog, the chicken, the monkey and the hamster, the rabbit still retains its leading role in this field of research (1). While numerous reports deal with the effects of the ingestion or injection of cholesterol on the cardiovascular system, there are only a few reports on changes occurring in plasma lipids. Anitschkow (2) noted an elevation of blood cholesterol in the cholesterol-fed rabbit and this basic observation was confirmed by subsequent workers in the field. However, in all of these studies cholesterol was fed in large quantities of fat, usually olive oil, a factor which in itself might have influenced the level of plasma cholesterol. Furthermore studies of blood lipids other than cholesterol were sporadic and of tangential interest only (3, 4, 5). To our knowledge there are only two reports concerning the effects on blood lipids of fat-free cholesterol feeding in the rabbit. One of these (6) concerned plasma cholesterol only while the other (7) added observations on non-cholesterol lipid fractions. In these studies amorphous cholesterol was fed in an aqueous suspension through a stomach tube. Twenty-four hours after administration of cholesterol a rise in all plasma lipid fractions was observed, with a progressive increase during continued cholesterol feeding. No statement was made, however, as to number of animals, number of controls, or variations of the various lipid fractions.

It seemed profitable therefore to study systematically the plasma lipid partition in a large number of rabbits during feeding of cholesterol without the addition of fat and without the use of a stomach tube in order to provide as uncomplicated an experimental environment as possible.

### MATERIAL AND METHODS

A total of 119 male rabbits was used for the study. The average age of the animals was 6 months, and the average body weight was 2 kg. Approximately one half of the animals were albinos, while the others were gray rabbits, and a few were "giant checkers." The diet consisted of purina rabbit pellets and water given ad lib. The daily food consumption ranged from 125-160 gm. per rabbit. The animals were weighed every 7-10 days.

The cholesterol-fed group was observed initially during a control period of

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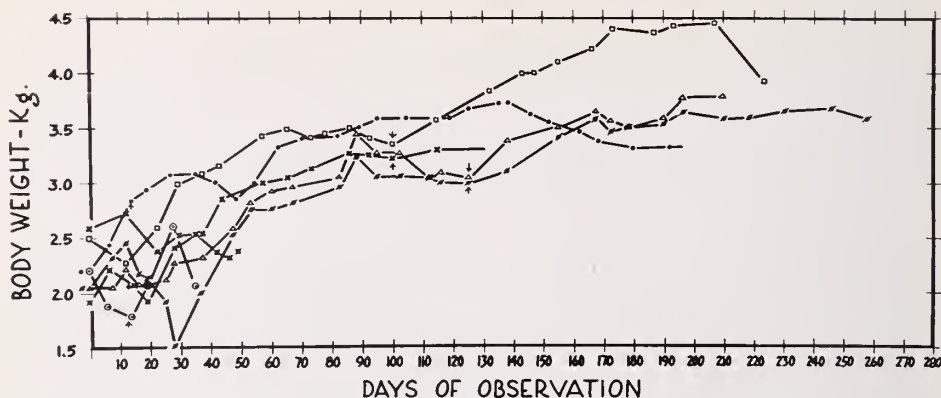


FIG. 1. Body weight of 7 rabbits during control period and during cholesterol feeding. Arrows indicate beginning of cholesterol feeding.

14–120 days. Only animals whose food intake was satisfactory and whose body weight during the control period was found to be constant or increasing were used for cholesterol feeding. The “cholesterol chow” was prepared in our laboratory: amorphous pure cholesterol U. S. P. (Armour Laboratories) was dissolved in a 10% solution in ether and was spread under stirring over thin layers of purina pellets; after the ether evaporated the cholesterol covered and infiltrated the pellets as a fine film of powder. The average daily intake of cholesterol per rabbit in the purina pellets was 1 gm. Cholesterol was thus fed in the regular diet, without the use of a fat vehicle or a stomach tube. The daily food consumption remained unchanged, and all animals showed a slow progressive gain in weight during the ingestion of cholesterol (Fig. 1). Under these conditions cholesterol was easily ingested and produced, as will be shown, severe alterations of blood lipids.

Blood was drawn at intervals from the marginal ear vein or the central ear artery. The animals were fasted for at least 16 hours before the blood was taken. The ears were shaved and immersed in hot water and a drop of heparin was placed in the syringe to prevent blood coagulation.

Total and free plasma cholesterol was determined by the original method of Schoenheimer and Sperry (8); lipid phosphorus by the Sperry modification of the Fiske-Subbarow method (9) (lipid phosphorus  $\times 25$  = phospholipid); total lipids by the gravimetric method of Bloor (10). Plasma neutral fat was estimated by subtracting the figures for total cholesterol plus phospholipid from that for total lipid. This simplified technique has been used previously by others (11) and by us (12).

#### *Plasma Lipid Partition in Controls*

All 119 rabbits served first as controls for a period of 2 weeks to 4 months. During this time one blood specimen was drawn in 96 rabbits, 2 in 16, and 3 or more specimens in 7 animals. A group was then fed cholesterol. The other groups were used for a subsequent study on the effects of cortisone, hydrocortisone and



TABLE 1  
*Plasma lipids of the control rabbits*  
 (All values expressed in mg/100 ml)

	NUMBER OF RABBITS	I <sup>1</sup>		II <sup>2</sup>	
		Mean	S. D. <sup>3</sup>	Mean	S. D. <sup>3</sup>
Total Plasma Cholesterol . . . . .	117	49	±24	54	±14
Esterified Cholesterol . . . . .	114	37	±18	38	±11
Phospholipids . . . . .	110	103	±27	102	±24
Neutral Fats . . . . .	102	197	— <sup>4</sup>	279	— <sup>4</sup>
Total Lipids . . . . .	102	350	±206	435	±166

<sup>1</sup> I—Single determination in 119 rabbits.

<sup>2</sup> II—Repeated determinations in 4 rabbits observed over a period of 3 to 4 months.

<sup>3</sup> S.D. = Standard Deviation.

<sup>4</sup> Since this is a calculated value, no S.D. was determined.

corticotropin on plasma lipids, sometimes in combination with thyroidectomy; these studies will be reported elsewhere.

The range of variations, the averages and standard deviations of the control animals are presented in Table 1. It is well known that the total plasma cholesterol of the rabbit is low when compared with that of man. It averaged 49 mg. per 100 ml. in this series; the free cholesterol represented 25% and the esterified fraction 75% of the total. There were considerable individual variations of the plasma cholesterol concentrations. The phospholipids averaged 103 mg. per 100 ml. of plasma in this series and were twice as high as the total cholesterol concentration. The high phospholipid:cholesterol ratio may be one of the reasons why spontaneous or senile atherosclerosis is so rarely found in this species. The total lipids and neutral fat of the plasma showed the greatest range of variation and averaged 350 and 197 mg. per 100 ml., respectively.

Although considerable variation was noted in the plasma lipid fractions from animal to animal, a certain constancy was characteristic for the individual rabbit over a period of many weeks. The last column of Table 1 presents average concentration and standard deviations of the lipid fractions in 4 rabbits observed over a period of 3–4 months. Similar observations were made by us in man and suggested the existence of a regulatory mechanism probably of hormonal nature (12). Using then the data of Table 1 one may consider for practical purposes and for the methods employed the average total plasma cholesterol of the rabbit to be approximately 50 mg., free serum cholesterol 15 mg., esterified cholesterol 35 mg., phospholipids 100 mg., total lipids 400 mg., and neutral fat 200–250 mg. per 100 ml.

#### *Plasma Lipid Partition During Cholesterol Feeding*

Twenty-eight rabbits whose food intake was satisfactory and whose body weight during the control period was found to be constant or increasing were used for the cholesterol feeding experiments. The plasma lipids were determined

TABLE 2  
*Effect of cholesterol feeding on plasma lipids of the rabbit*  
 (All values expressed in mg/100 ml)

	Control	1 Mo	2 Mo	3 Mo	4 Mo	5 Mo	6 Mo
Total Cholesterol							
Mean . . . . .	49	641	914	1476	1179	1149	1213
S.D. . . . .	±24	±329	±441	±768	±455	±358	±768
Esterified Cholesterol							
Mean . . . . .	37	458	669	1141	885	854	896
S.D. . . . .	±18	±230	±356	±594	±357	±451	±551
Phospholipids							
Mean . . . . .	103	330	413	460	462	460	512
S.D. . . . .	±27	±126	±137	±155	±196	±206	±230
Neutral Fats							
Mean <sup>1</sup> . . . . .	198	741	893	1094	1048	853	842
Total Lipids							
Mean . . . . .	350	1712	2219	3030	2689	2462	2567
S.D. . . . .	±206	±788	±925	±1457	±1313	±1157	±1448

S.D. Standard deviation

<sup>1</sup> Since this is a calculated figure no S.D. is done

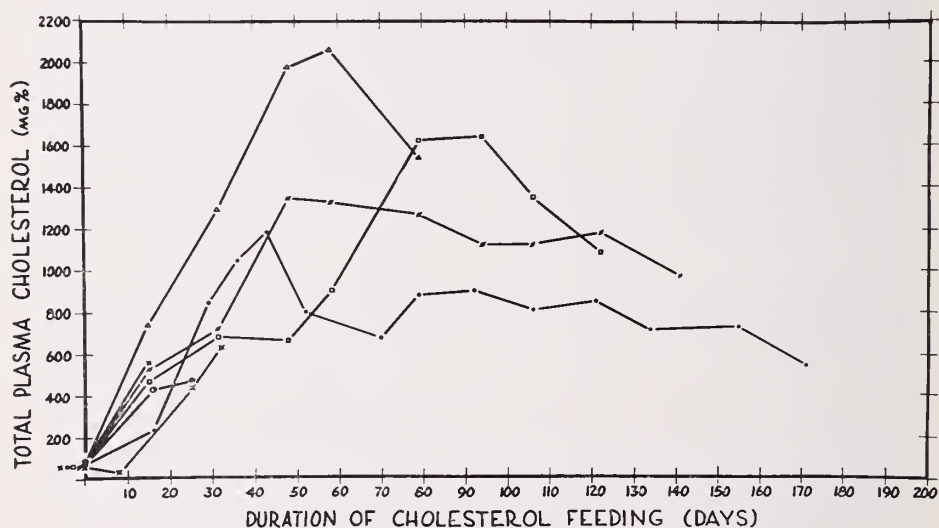


FIG. 2. Effect of cholesterol feeding on plasma cholesterol levels in 7 rabbits.

at regular intervals of 2 weeks in these animals while they were being fed cholesterol.

The steady rise in all lipid fractions which occurred for the first 3 months, and the subsequent leveling off at slightly lower levels is shown in Table 2. Again there were considerable variations in all lipid fractions from animal to animal. After 3 months of cholesterol feeding the average total plasma cholesterol rose to 30 times normal; free plasma cholesterol and esterified cholesterol increased

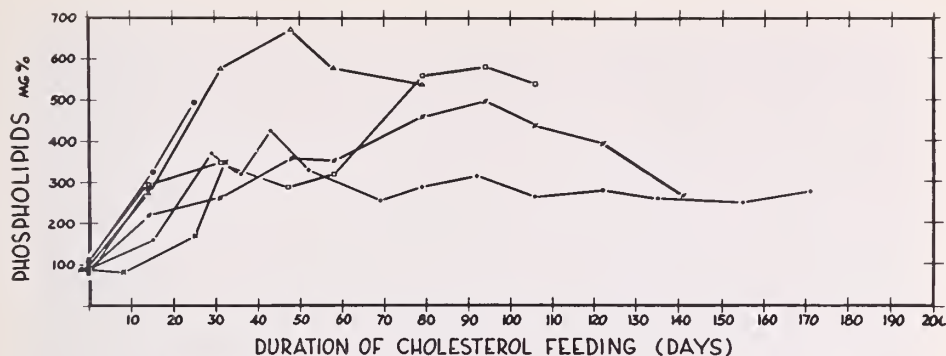


FIG. 3. Effect of cholesterol feeding on plasma phospholipid levels in 7 rabbits.

similarly. The elevation of plasma phospholipids fell far behind that of plasma cholesterol. After 3 months of cholesterol feeding the average phospholipids reached 4.6 times the control; an additional moderate elevation was seen after 6 months. The differences observed during cholesterol feeding between plasma cholesterol and phospholipid elevation are best expressed by the phospholipid-cholesterol ratio which showed a striking change from 2.1:1 during the control period to 0.3:1 during the period of cholesterol feeding. The average total plasma lipids rose to 8.7 times the control after 3 months of cholesterol feeding. After 4 to 6 months the level decreased moderately. The plasma neutral fat increased to 5.5 times normal in 3 months. The elevation of neutral fat was associated with lactescence of the plasma. There was a slow and slight decrease of the plasma neutral fat in the 5th and 6th months. Figs. 2 and 3 illustrate the alterations of plasma cholesterol and phospholipids in 7 animals.

#### DISCUSSION

The pronounced changes of plasma lipids which follow prolonged administration of cholesterol in the rabbit were presented. These changes occurred without the use of a fat vehicle or stomach tube, thus indicating the ability of the rabbit to absorb large quantities of pure cholesterol from the gastro-intestinal tract.

The elevation of plasma cholesterol is the consequence of the ingestion of dietary cholesterol. The elevation of plasma phospholipids is not as great as that of plasma cholesterol. This may indicate that the mobilization and synthesis of phospholipids by the rabbit cannot keep pace with the massive invasion of cholesterol into the organism. The same statement is probably permissible in regard to neutral fat mobilization and synthesis, which also remains far behind that of the elevation of plasma cholesterol.

These observations in the herbivorous rabbit permit no conclusions for the carnivorous dog or omnivorous man. Cholesterol feeding, even in excessive amounts, leads only to moderate elevations of plasma cholesterol in these species.

A number of the animals developed deep ulcerations of the paws during cholesterol feeding (Fig. 4). These ulcerations contained cheesy material of a high cholesterol content (950 mg. per 100 gm.). The histological examination revealed



FIG. 4. Ulcerated xanthomas as illustrated in this figure were found in some animals after prolonged feeding of cholesterol.

xanthoma-like skin lesions with secondary infection and abscess formation. A detailed description of these lesions will be presented elsewhere.

#### SUMMARY

The plasma lipid partition was studied in 119 rabbits who were maintained on a diet of purina chow. Twenty-eight of these rabbits were then carefully observed during a period of cholesterol feeding.

The average total plasma cholesterol of this large control series was 49 mgm. per 100 ml. with 25% free cholesterol and 75% esterified. Phospholipids averaged 103 mgm. per 100 ml. Phospholipid:cholesterol ratio was thus 2.1:1. Total lipids averaged 350 mgm. per 100 ml., and neutral fat 197 mgm. per 100 ml.

Daily oral ingestion of 1 gm. of cholesterol for 3 months resulted in an average total plasma cholesterol of 1476 mgm. per 100 ml. which was 30 times the control level. This elevation affected the free and esterified fractions equally. The phospholipids rose to an average of 460 mgm. per 100 ml., 4.6 times the control level. The phospholipid-cholesterol ratio decreased from 2.1 to 0.3. Total lipids rose to 3030 mgm. per 100 ml., 8.7 times the control. Neutral fat increased 5.5 times to 1094 mgm. per 100 ml. At this high level of serum lipids, the serum appeared milky.

These marked alterations of the serum lipids were produced in the rabbit by feeding pure cholesterol without a fat solvent and without the use of a stomach tube.



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# INTERATRIAL CONDUCTION DEFECTS ASSOCIATED WITH SUPRA-VENTRICULAR TACHYCARDIA IN INDIVIDUALS WITHOUT ORGANIC HEART DISEASE\*

M. B. WALTERS† AND A. GRISHMAN

Paroxysmal tachycardia of supraventricular origin may originate from the atrio-ventricular node or allied specialized muscle tissues and then is referred to as nodal tachycardia. Whether ectopic arrhythmias may also result from foci within the atrial musculature itself is not known and actually not pertinent to the problem discussed here. Similarly, atrial flutter and fibrillation may be encountered as the sustaining mechanism of paroxysmal tachycardia. Here again the actual physiological alterations which give rise to the one form in preference to the other are of little importance to the subject of our discussion.

Having observed a large number of cases with paroxysmal tachycardia we were impressed by the fact that often the atrial complexes were abnormal in individuals without detectable organic heart disease or clinical or laboratory evidence of hyperthyroidism.

The electrocardiographic tracings of 8 patients have been selected for the presentation of our observation. In all a careful physical and radiographic examination failed to reveal any evidence of organic heart disease. None showed any clinical or laboratory evidence of hyperthyroidism nor did their history suggest underlying coronary artery disease. Between attacks of paroxysms the patients were asymptomatic.

During the periods of sinus rhythm the most commonly noted abnormality of the P-wave was notching and prolongation; in some there was also a tendency to increased voltage. Such abnormalities were observed while the patients were not receiving medication.

## COMMENT

The abnormal P-waves seen in the electrocardiogram of some patients who are subject to attacks of paroxysmal tachycardia and who have no other objective evidence of heart disease, would indicate the presence of some abnormality of the course of the excitation wave through the atria. Since the P-waves were broader than normal and notched it is suggested that an interatrial conduction defect exists in these cases as a result of an affection of the atrial musculature. Such a process might take the form of scarring of a portion of the atrial myocardium as a result of infectious processes like scarlet fever, diphtheria, etc., or, possibly as a result of a subclinical degenerative process due to coronary artery disease or a congenital abnormality of unknown nature.

Abnormal interatrial conduction has excited little comment in the literature. Lewis, Meakins and White (1), tracing the course of the excitatory process through the atria by the method of primary negativity postulated that the

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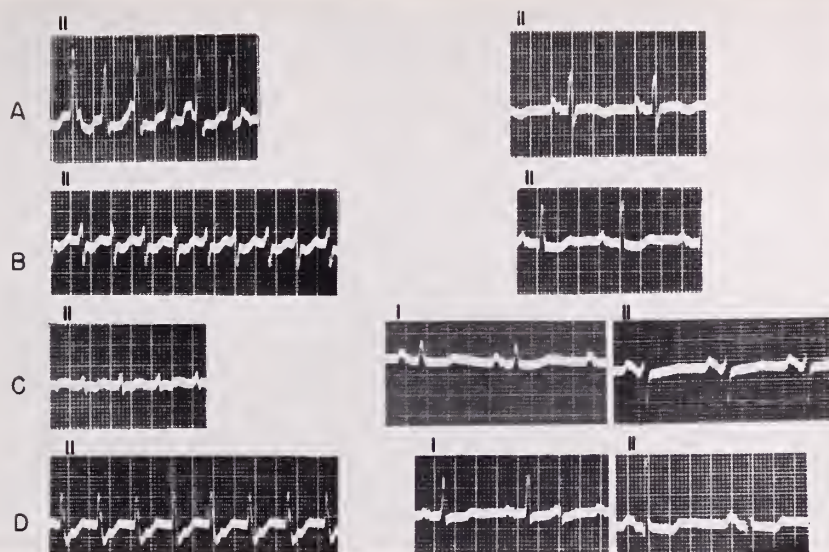


FIG. 1. Broad and notched P-waves, while regular sinus rhythm prevails. A: Nodal rhythm with reentry leading to tachycardia. B, C, D: Nodal tachycardia.

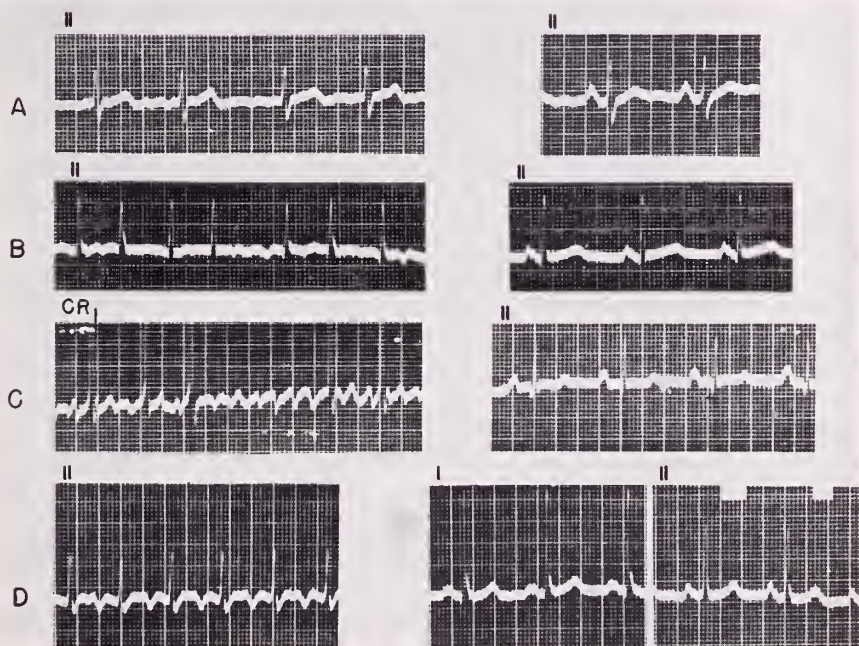


FIG. 2. A, B: Atrial fibrillation. C, D: Atrial flutter.

impulse radiates from the sino-atrial node with equal velocity in all directions apparently without the aid of specialized pathways. Although such Purkinje fiber-like structures have been established in the horse atria similar evidence in humans is not available (2). Bachmann produced delayed left atrial stimulation by clamping the interatrial band which he regarded as the most important path of conduction between the two atria (3, 4). Scherf and Shookhoff (5) observed altered atrial complexes in animal experiments after a run of induced atrial extrasystoles. This they regarded as a fatigue phenomenon of interatrial conduction. Holzmänn in discussing the possibilities leading to interatrial conduction disturbances lists mainly those associated with left or right atrial enlargement (2). He also enumerates, however, autonomic imbalance and impaired circulation as possible causes. Although he mentions the transient appearance of abnormal P-waves after paroxysmal tachycardia he does not describe similar changes for the interval period.

The finding of abnormal P-waves in healthy persons subject to attacks of paroxysmal tachycardia (nodal tachycardia, atrial flutter and fibrillation) might be an indication of the presence of localized block in the atrial myocardium possibly due to an abnormal pathway of the excitation wave through the atria. Whether this is the result of a congenital anomaly or the result of an intercurrent disease leaving no other detectable traces of cardiac alterations can not be determined. An area of localized "block" would cause the excitation wave to take a more circuitous route and might set up a localized circular spread of the excitation wave. A re-entry of the stimulus to form a focus of a circulating wave might be set up under appropriate circumstances—such as with a slight slowing of the conduction rate in the atrial musculature under altered autonomic balance.

#### SUMMARY

Attacks of supraventricular tachycardia may occur in healthy people with no evidence of organic heart disease or hyperthyroidism. In a number of such patients abnormal notched and widened P-waves are present in the electrocardiogram during periods of sinus rhythm. These changes were observed in between paroxysms and also without the influence of drugs like digitalis, quinidine sulfate, etc. The abnormality is thought to be directly related to the patient's tendency to paroxysmal supraventricular tachycardia and thought to present an interatrial conduction defect.

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# NUMERICAL EVALUATION OF OCULAR SIGNS OF ESSENTIAL HYPERTENSION\*

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The validity of Wagener's (1, 2) classification of the hypertensive changes in the fundus into four grades is universally accepted. It is, however, well recognized that the limits between one grade and the next, are not sharply demarcated, but rather overlap.

Of particular interest to the author was the impression that the fundus changes were evident in hypertensive disease even before Grade I was established. It seemed that the area of incipient hypertensive disease demanded further scientific investigations, the results of which promised to be valuable in the field of preventive medicine. Whatever advances were to be made, they seemed to be as important in the area of beginning hypertension as in the later stages. The inference to be made from the well-known parallel relationship between the degree of retinopathy and the severity of the hypertensive disease was that one might expect to find enough early changes in the fundus which would permit the examining physician to make a diagnosis of an incipient stage of established essential hypertension. In other words, one is justified in assuming that there is a transition stage between the normal fundus and the picture seen in Grade I. If pathognomonic objective signs could be established, and if they could be recognized with an unequivocal degree of certainty, it would be of great value in establishing an early diagnosis. For example, it is often stated that in eclampsia, the narrowed vessels in the retina return to their previous normal appearance when the arteriolar spasm is relieved. The author, from his own observations, believes that such a dictum should not be permitted to go unchallenged. On the contrary, years after the eclampsia had been cured, persistent alterations in the caliber of the arterioles were seen in many cases, even though the blood pressure had returned to normal readings.

In essential hypertension also there are residual, irreversible changes in the arterioles to be seen during the periods of remission, when the blood pressure levels may have dropped to relatively normal limits. If we exclude the so-called malignant type, essential hypertension is characterized clinically by states of exacerbation (when the diastolic pressure is elevated), and the periods of remission, when the diastolic pressure is lowered, and may even return to normal levels. These alternating phases are characterized by a gradual progressive increasing degree of severity. It is generally accepted that it is the height of the diastolic pressure that is proportional to the severity of the hypertensive changes in the fundus (3).

In a paper, presented before the Eye Section of the American Medical Association Meeting in June, 1953, the author (4) reported a coefficient of correlation

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(0.87) between the diastolic pressure and the sum of the numerical evaluations of the different hypertensive signs in the fundus. The data were collected from a series of 100 cases, studied at The Mount Sinai Hospital. A random mixture of hypertensive and non-hypertensive cases were selected by the Resident in the course of routine requests for fundi examinations. If the observer had received any inkling of the patient's history, physical findings, or blood pressure readings, the case would not be included in the study. The description of the findings, including a tentative ophthalmoscopic diagnosis, were dictated to the Resident, who wrote them into the hospital record. Sometime later, the record was studied for further pertinent data. In this way, an unprejudiced collection of signs was assured. Previously, it had been decided to use only the following signs which were by definition unequivocally objective and, therefore, not open to any doubt on the part of the author himself or any other observer.

#### OBJECTIVE OCULAR SIGNS OF ESSENTIAL HYPERTENSION

##### A. *Optic Nerve Head:*

1. Blurring (B);
2. Edema (E);
3. Elevation (L).

##### B. *Retinopathy:*

1. Ischemic Infaret or exudate (X);
2. Hemorrhagic Infaret (H);
3. Edema Residue or Degeneration (D).

##### C. *Arteriolar Narrowing:*

1. Uniform Narrowing (UN).
  - a. One segment between the branchings;
  - b. More than one segment (A1, A2, A3, and/or A4).
2. Irregular Narrowing (IR).
  - a. Segment between branching:

###### 1) Distal Tapering (DT).

The segment of the arteriole is broader proximally and narrowed peripherally, in a gradual manner, giving the appearance of a truncated cone.

###### 2) Proximate Tapering (PT).

The reverse of distal with the narrowed portion proximal, giving the appearance of an inverted truncated cone.

###### 3) Hourglass Narrowing (HG).

The focal narrowing occurs in some portion of a segment.

###### 4) Beading (Bd).

More than one focal narrowing in one or more segments.

###### b. The branching itself.

###### Narrowed fork (NF):

###### 1) One-armed Fork (F1).

Stem and one arm of the branch normal in caliber, but the other arm narrowed.

## 2) Distally Narrowed Fork (DF).

Stem normal, but both arms of the branching narrowed.

## 3) Proximally Narrowed Fork (PF).

The parent stem is definitely narrowed but the branches themselves are normal in caliber.

D. *Venule Narrowed (VN)*.E. *Arteriovenous Crossing Pathology (AVX)*.

## 1. Displacement

a. Anterior; (da)

b. Posterior; (dp)

c. Lateral (dl).

## 2. Banking (bg).

Certainly, such signs as hemorrhage, exudates, degeneration, and neuropathy were definite enough. On the other hand, all signs dealing with color values or light reflexes, were judged to be controversial because they were too subjective to be agreed upon by all observers. For the same reason, the degree of uniform narrowing of the arterioles expressed as one-fourth or one-half of the normal caliber could not be used. The simple fact of an arteriole being narrowed at all (provided that it was unquestionably so to any examiner) was considered to be more trustworthy as an objective sign than the degree to which it was narrowed.

For investigative purposes, the arteriolar system was divided into segments and branches. The first segment at the disc was named A1, the next A2, the third A3, and the fourth A4. For example, if the fourth segment was narrowed, it was recorded as A4N. Sometimes the narrowing was so marked as to render visibility of the segment difficult; the "N" was then encircled. No detailed study of the segment beyond the fourth was considered practical. An arteriovenous crossing received its numeral from the arteriolar segment involved. For example, AVX3 indicated a vein, crossing the third segment of the arteriole. The position of any lesion in the retina was located for further reference along meridians radiating from the optic nerve head by Roman numerals corresponding to the hours of the clock. The distance from the optic nerve was designated by an exponent which expressed the number of the disc diameters which the lesion was away from the optic nerve along that particular meridian. Thus, HV<sup>3</sup> meant a hemorrhage in the retina, three disc diameters away from the nerve along the 5 o'clock meridian.

When the caliber of the retinal arterioles in the fundus is considered as an objective physical sign, many interesting questions in physiological optics arise. Suffice it to say that most of them belong to the considerations of optical illusions and need not be expounded here at length. However, two ideas may be used to clarify the objective quality of the relatively easy recognition of a pathological uniform narrowing. The normal arteriole gradually diminishes in caliber from the optic nerve to the periphery in such a way that the actual difference between any segment diameter and that of its branches does not attract attention due to the physiological optics governing the appearance of a tube which divides by an acute angle into two equal branches. The vessel is seen as if it were a two dimensional ribbon in a flat plane. For example, if one would snip the end of a ribbon

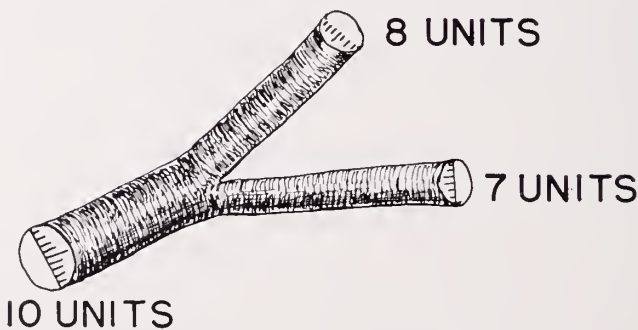
(to simulate two equal branches), one could easily see that the "branches" appeared to be narrowed, because the differences would be obvious. In the arteriole, however, the observer is dealing with a tube in a spherical plane and the relationship between stem and branch is a volumetric one. The sum of the diameters of the branches actually add up to more than the diameter of the parent stem. Therefore, as the eye of the examiner travels from the arteriolar stems to its branches, the differences in caliber (though apparent if they were critically studied), are slurred over. The attention of the observer is not arrested in the act of scanning the vessels in the routine examination. In other words, the difference is not obvious.

Measurements, made from projected photographs of the normal retinal arterioles, show that the relationship of the diameter of the parent stem to the diameter of the immediate branches has a normal ratio of 10:8 or 10:7 (fig. 1). The point to be emphasized here is that pathological narrowing of a branch is "obvious" when the ratio is 10:6 or less, since such a difference is enough to arrest the attention of the observer immediately, almost without study on his part. For the purpose of defining an objective clinical sign, this quality of the term "obvious" is quite fortunate.

#### OBJECTIVE ARTERIOLAR SIGNS

Arteriolar narrowing consists of two types: uniform and irregular (or focal). The definition of obvious narrowing, which was described in the foregoing, takes

## NORMAL BRANCHING



## STEM RELATED TO BRANCHINGS

10:8 OR 10:7

FIG. 1. The normal arteriole seems to divide in a gradual manner because the diameter of the stem is related to the diameter of the branches in the ratio of 10:8 or 10:7, and the eye passes from one to the other without noticing the differences because the difference is not sufficient to obtrude itself upon the observer.



TABLE I

*Percentage frequency of hypertensive signs in 67 cases with elevated diastolic pressure*

SIGNS	NO. OF CASES	PERCENTAGE OF FREQUENCY
Uniform narrowing of 3rd segment (A3N) . . . . .	55	82%
Uniform narrowing of 2nd segment (A2N) . . . . .	52	78%
Uniform narrowing of 4th segment (A4N) . . . . .	44	66%
AVX Banking (AVXb) . . . . .	43	64%
Uniform narrowing of 1st arteriolar segment (A1N) . . . . .	43	64%
AVX Concealment of vein (AVXc) . . . . .	38	57%
Lateral displacement of vein (AVXd) . . . . .	35	52%
Vein narrowed (VN) . . . . .	35	52%
Arteriolar reflex increased (Rfx +) . . . . .	31	46%
Retinal hemorrhage . . . . .	27	40%
Irregular narrowing of arteriole (IR) . . . . .	24	36%
Retinal exudate (ischemic infaret) (X) . . . . .	23	34%
Distal tapering (DT) . . . . .	21	31%
Edema of nerve head (E) . . . . .	17	25%
Blurred nerve margin (B) . . . . .	16	24%
Proximal tapering (PT) . . . . .	15	22%
Posterior displacement of vein (AVxp) . . . . .	13	19%
Degenerative spots in retina (edema residue) (D) . . . . .	12	18%
Distal fork narrowed (FN) . . . . .	11	16%
Elevation of nerve head (L) . . . . .	11	16%
Hour-glass narrowing (HG) . . . . .	9	13%
Beading (Bd) . . . . .	6	9%
Arteriolar reflex diminished (RF-) . . . . .	5	7.5%
One arm of fork narrowed (F1N) . . . . .	4	6%
Copper-wire artery (C) . . . . .	3	4.5%
Proximal tapered fork (PF) . . . . .	2	3%
Silver wire reflex (S) . . . . .	2	3%
Star-shaped figure in the macula . . . . .	1	2%

care of all segments except the narrowing of the first segment which is the only sign used in this study, that requires previous experience for comparison with the normal.

Irregular narrowing, or focal narrowing consists of two groups: the first one, relating to the segment, and the second one, relating to the branch itself, or simply, the fork.

After 100 cases had been accumulated, it was found that the average number of signs per case increased with the height of the diastolic pressure (fig. 1). Seventeen cases were relatively normal. Of the remaining 83 cases, 67 had increased diastolic readings. The distribution in the latter group of the signs in the fundus is shown in Table I. The most common sign was uniform narrowing of the arterioles. Arteriovenous disease came next in frequency. The sign of the narrowed venule, although occurring in 52 per cent of the hypertensive cases, had heretofore not been stressed in the literature. It was interesting to note that irregular narrowing occurred in 24 cases, or 36 per cent. The frequency of irregular narrowing (or focal narrowing) points up the importance of the sign, since it is

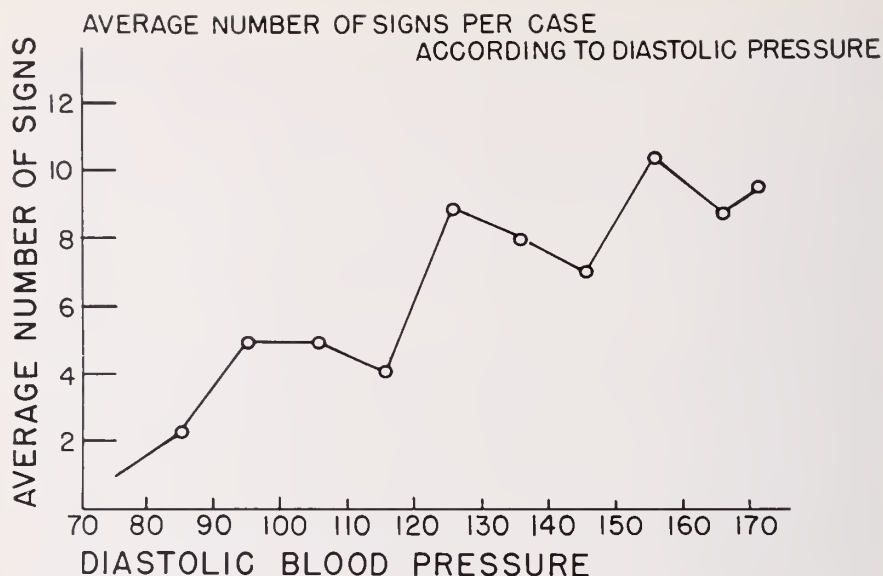


FIG. 2. In this series of 100 cases there is a direct relationship between the average number of signs (each different sign counted but once, no matter how frequently it occurs in the fundi), and the height of the diastolic pressure.

the most easily recognizable. Its presence serves to alert the examiner to the possibility of uniform narrowing which may be more easily missed during the routine examination.

The conclusions drawn from this series do not necessarily hold for the general population, because of the small number of cases, but should be considered as an adequate sampling carefully studied, and scrupulously evaluated.

#### STATISTICAL CONSIDERATIONS

The raw data were considered in the following steps: 1. A base line of the upper limits of normal diastolic pressure was postulated from Master's (5) data, adjusted for sex and age, for the general population. 2. The highest diastolic pressure recorded in the hospital charts then was converted into a percentage deviation (plus or minus) from the upper limit of normal diastolic pressure, according to age and sex. 3. The third step was to find the average of the percentage deviation for each physical sign. 4. These averages were then arranged in groups dependent upon the anatomical relationships, such as: neuropathy, retinopathy, uniform narrowing, irregular narrowing, arteriovenous disease, and the narrowed venule. 5. The averages found for each group were reduced to simple round numbers by an arbitrary numerical factor which reflected the clinical insight of the author in order to express the relative importance of the sign. 6. In this way, one numerical value was assigned to each sign, no matter how frequently that sign occurred, in a particular case, so that the sum of these weighted signs would give an indication of the severity of the fundus picture. When Dr. Feitelberg, to whom I am indebted for his suggestions in handling the raw data and for his statistical cal-

## WEIGHTED VALUES OF SIGNS

NERVE	RETINA	ARTERIOLES		VEINS	AVX
		UN	IR		
B-9	X-8	A1	2	DT-3	A1-3
E-11	H-9	A4	3	PT-5	A2-5
L-13	D-10	A1+3	6	HG-7	A3-7
		A2+3+4	9	NF-9	A4-9
		A1+2	12		
		A1+2+3	15		
		A1+2+3+4	18		
		A1+2+3+④	21		

UN VALUES DOUBLED  
IF E OR L PRESENT.

FIG. 3. The weighted values of a sign counted but once, no matter how frequently it occurs in the particular case. B. represents a blurred nerve margin; E. an edematous nerve margin; L. elevation of the nerve head; X. ischemic infarct or exudate; H. hemorrhage; D. edema residue or degeneration; UN. uniform narrowing; A1. first arteriolar segment; A1 + 2 + 3 + 4, all four segments narrowed; A4. encircled, the fourth segment not seen or difficult to be visualized; IR. irregular narrowing; DT. distal tapering; PT. proximal tapering; HG. hourglass narrowing; NF. any part of the fork narrowed; VN. narrowing of the venule; AVX. arteriovenous crossing pathology comprising both displacement and banking.

culations, finally calculated the coefficient of correlation from the raw data, he found it to be 0.87 with a standard deviation of  $\pm 0.027$ . 7. The weighted signs were recently increased so as to avoid the use of a multiplication factor originally reported.

It followed that from such a high degree of correlation, it should be possible to estimate a patient's diastolic pressure from the sum of the weighted signs. A discrepancy appeared in those cases in which the nerve head showed either edema or elevation in that the estimate of diastolic pressure was too low. It was clearly evident clinically, that patients with involvement of the nerve head were more seriously ill than those who had arteriolar signs alone. Finally, it developed that, if in these cases the arteriolar signs were given twice the value for uniform narrowing found in cases without involvement of the nerve head, the greater part of the discrepancy disappeared and the estimate of pressure more nearly approached the actual readings. Figure 3 shows the revised values for each sign (counted but once) in the hypertensive fundus which, when added to 85 (representing the upper limit of normal diastolic pressure), gave the estimate of that diastolic pressure which the patient had suffered for a considerable length of time, somewhere in his recent or remote past. It is believed by the author that such an estimate of pressure is at least within the limits of error which is inherent

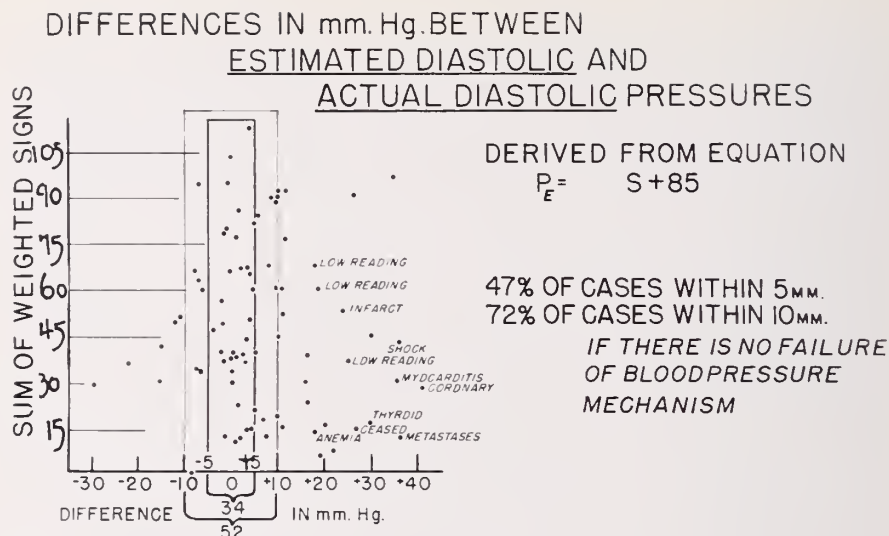


FIG. 4. Scatter diagram of the discrepancies considered in mms. of mercury between the diastolic pressure estimate from the sum of the signs in the fundus and the actual diastolic pressure. In the equation  $P_E$  represents the estimate of diastolic pressure level somewhere in the patient's recent or remote past. It may coincide with the patient's present diastolic pressure.  $S$ , the sum of the weighted signs each counted but once, 85, represents the upper limit of normal diastolic pressure.

in the very technique of taking the blood pressure readings with the sphygmomanometer. Finally, Figure 4 shows the relationship between the estimates of diastolic pressure (derived from the original weighted signs) in the abnormal cases and the actual sphygmomanometer readings of the diastolic pressure. Of the 83 abnormal cases, 34 were estimated within 5 mms. of the actual diastolic pressure, or in 41 per cent of the cases. Fifty-two cases were estimated within 10 mms., or 62 per cent. If the cases in which there was a failure of the blood pressure mechanism (such as coronary disease etc.) and those cases where the blood pressure reading used in the raw data was lower than the highest in the chart are eliminated from consideration, it was seen that 40 per cent of the cases were estimated within 5 mms. of the actual diastolic blood pressure, and 72 per cent of the cases within 10 mms.

#### DISCUSSION

The values of the weighted signs are presented only as a successful attempt to assign numerical values to the hypertensive ocular signs in the manner of Wilson (6). For these findings to apply to the general population, it will be necessary to study a far larger number of cases, and it would be instructive if a different series of cases would be evaluated by other observers. The arteriovenous crossing probably needs more investigation.

It is interesting to speculate about those cases in which there were either too little or too great an estimate of the diastolic pressure. Perhaps it is not presumptuous to assume that, if the estimate made of diastolic pressure is greater than

the actual diastolic reading, the patient (although undoubtedly a hypertensive) is in a period of remission or is suffering from cardiac dysfunction. Conversely, if the estimate is too low, the clinician might entertain the idea that the patient's blood pressure reading has a psychogenic basis for its high level.

#### SUMMARY

1. A classification of objective signs of hypertension in the fundus is presented.
2. A definition of "obvious" uniform narrowing of the retinal arteriole is made and the importance of irregular narrowing is stressed.
3. An attempt to develop a numerical system of estimating diastolic pressure from the ocular signs is offered for consideration.
4. A point is made that the retinal changes give evidence of past elevation of diastolic pressure even during periods of remission.
5. The examination of the fundus may lead the physician to suspect psychological factors if the blood pressure readings are higher than those expected from the retinal changes.
6. The converse should lead to the suspicion of cardiac dysfunction or shock.

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## PATHOLOGIC ANATOMY IN MODERN MEDICINE<sup>1, 2</sup>

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In his famous farewell address Rokitansky could justly assert that he had pursued pathologic anatomy as a scientific vocation aimed at fertilizing clinical medicine; and his eulogist, Heschl, epitomized Rokitansky's contribution to medicine by stating that "through him alteration of structure became the focal point of the problem of disease." But forty years later, one reads that pathologic anatomy is only dead-house pathology that can contribute nothing to the understanding of disease, which is a problem of disturbed function and must, therefore, be investigated with the methods of physiology. Though in subsequent years the contributions of pathologic anatomy were again more appreciated, there is no question that the esteem it enjoyed in the 19th Century has never been reached again. The pathologic anatomist who has been raised in the traditions of the classical era must question the reasons for this decline. He must try to understand whether the lessened appreciation is due to deficiencies inherent in the method or due to lack of leadership which, in turn, might have been the result of the great attraction exercised by the more dynamic approach of physiology, supported by the rapidly advancing methodology of biochemistry and biophysics. The critical investigation demands a clarification of the essential aims of the anatomical concept in pathology, and necessarily must trace them back to their origin. It must pursue its object in a detached manner and with due consideration of the values of different approaches to pathology in its broadest sense: the comprehension of disease.

Anatomical observations of morbid states of the human body were recorded after anatomy had come into its own through the influence of Vesalius and his school. One of the first is the report of William Harvey of the post-mortem findings of Thomas Pratt, and Baglivi's description of the necropsy of Malpighi. A collection of autopsy records of Bonetus has been assembled in his *Sepulcretum*, published in 1705, and Morgagni drew freely from these and other sources. However, they were not only rare, but also merely individual descriptions without theoretical abstraction. The immortal contribution of Morgagni lies not so much in his admirable records of clinical and anatomical observations, but far more in his conceptual generalization expressed in the title of his work, "On the Seat and Cause of Disease as Investigated by the Anatomist."

The advance of Morgagni's theory can only be appreciated if one considers it in relation to the epistemologic state of contemporary medicine. The knowledge of disease was still dominated by Hippocratic tradition and purely descriptive. Ideas of pathogenesis were still under the influence of the Platonic, mystical, four Humores embellished by vague, mechanistic and chemical speculations. By

<sup>1</sup> 18th Harrison S. Martland Lecture delivered before Essex County Pathol. Anat. Society, December 10, 1953.

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correlating the fleeting manifestations of disease, as seen in the living, with the tangible organ alterations in the dead body, Morgagni established the first scientific system in medicine. This anatomical concept has become so ingrained in our thinking that we are hardly aware of its application in our present-day medical operations. But it is no exaggeration to assert that our deliberations and methods in the diagnosis of disease are, even today, largely directed toward a visualization of the underlying anatomic alteration. Morgagni's principles became the foundation of diagnostic medicine as it developed in the 19th Century. The great clinician-pathologists of France and England, Laennec, Bretonneau, and Bright, the famous Vienna School of Medicine led by the clinician, Skoda, and guided by Rokitanski, were amongst the first who helped to complete the work. Even Semmelweis' great discovery rests upon Morgagni's inspiration. Yet in the light of subsequent developments, it is evident that Morgagni's anatomic concept could not accomplish what he had promised. The ultimate cause of disease could not be revealed by anatomic investigation only. By correlating clinical symptoms with structural alterations, pathologic anatomy could better circumscribe morbid entities which were ill-defined by mere clinical manifestations. But this descriptive characterization can neither account for the "why" nor explain the "how" of the alteration of form and function characteristic of disease, which is the ultimate goal of pathology. This inadequacy was brought to attention by the anatomist Henle who asserted that medicine under the influence of pathologic anatomy has only exchanged the old clinical terms for new ones which stand for the anatomical alteration. How appropriate were Henle's words of caution as one reads in Soemmering's preface to the translation of Baillie's "Morbid Anatomy" the following smug sentence: "Frequent experience has taught me that one easily acquires a precise and real concept of a disease by careful investigation of the morbid alteration." Soemmering was one of the leading German physicians of the early 19th Century and one can assume that his point of view was shared by a majority of his colleagues, the more so since Rokitansky's influence dominated the development of medicine in Austria. This attitude of appreciating pathologic anatomy merely because of its usefulness for clinical diagnosis would have aborted the future development of medicine. But, fortunately, natural science was already firmly established, and the inquiry into cause was the dominant force in its explorations. Mere static observation was no more sufficient. Life as a process came under scrutiny; anatomy was linked with physiology, and pathologic anatomy was forced into a dynamic direction. It is possible that this development would have gradually taken place. Actually, however, it was the genius of one man who gave the new orientation to pathologic anatomy and who expanded the system of Morgagni. Rudolf Virchow is often regarded as the first histo-pathologist, and his cellular pathology as a mere revival of Morgagni's organic pathology (*Rindfleisch*). According to this idea, pathologic histology shows how the coarse alterations of organs revealed by pathologic anatomy are founded upon certain changes of tissue constituents. But Virchow's vision was not bounded by the descriptive characterization of cell changes. While he believed that the seat of disease was in the cells, the

elementary constituents of the living body, his aim was the comprehension of the process which underlies their alteration of form and function in disease. This is the fundamental idea which animates his entire life work and which he precisely expressed in the enthusiastic articles of his youth and the judicious statements of his advanced age. "To understand the evolution of morbid states—that is the contribution of science and the objective of thinking man." This was the principle which guided him as pathologic anatomist and inspired his immediate disciples and those who followed him. Today, in a period of expansion and specialization, we are hardly aware that medical investigation is still under the influence of this "regulative principle" as Royce expresses it. As the modern pathologic anatomist tries to reproduce structural alteration characteristic of human disease by animal experiment, he should not only recall Virchow's experiments on thrombosis and embolism, but especially his introductory remarks that the experiment is only the control for the pathologic anatomic conclusion reached by unbiased anatomic perception. As anatomic pathology of today tries to penetrate the mysteries of cellular abnormality by the application of histochemistry, or utilizes ultra-centrifugation for the identification of elementary constituents of the cell, one is reminded of the words of Virchow: "By calling attention to the cell, I desired to force the investigators to determine the process within the cells, and it was quite evident that this exploration was to aim at the discovery of the physical and chemical foundation upon which manifestation of life and vital activity rest." While the influence of the great physiologists and bacteriologists of the 19th Century, such as Bernard, Ludwig, Pasteur, and Koch, upon the development of clinical medicine cannot be evaluated too highly. Rudolf Virchow's concise definition of disease as the course of vital phenomena under altered conditions remains, even today, an epitome of the highest precision. It has already been asserted that Virchow must not be regarded merely as a profound pathologic anatomist and histologist. His own words refute such an estimate when he maintains that "chemical and physical investigation is of a higher order than anatomy and morphology". But he affirms the fundamental value of anatomy for the progress of medical science with the statement "that at all times, permanent advances were determined by anatomic disclosures, and that each greater epoch was initiated by a series of important discoveries of the structure and equipment of the body". Accordingly, Schwann's discovery of the cellular constitution of the animal body became the corner-stone upon which Virchow could build the morphologic-physiologic system of his cellular pathology.

The evolution of science in general, and that of medicine in particular, can be understood only if one correlates it with the philosophical climate of the contemporary period. As Burkhardt says: "there are men who are by nature mirrors of what surrounds them". Morgagni's association of ill-defined symptoms of disease with tangible organ changes as perceived by anatomic observation, seems to me to rest upon the prevailing epistemology of the 18th Century, Francis Bacon's empiricism, and John Locke's theory of cognition by sense perception. In fact, Morgagni's conclusions were foreseen by Bacon who, pleading for the performance of necropsies, maintained that "in the difference of the

internal parts are also found the immediate causes of many diseases". The influence of Bacon upon Morgagni is quite obvious in the two indexes appended to the last volume. These are the catalogues of morbid manifestations, clinical as well as anatomical, according to Bacon's precept to "prepare as a foundation for the old (interpretation of nature) a complete and accurate natural history". But in the years subsequent to the publication of Morgagni's work the foundation of Locke's philosophy, which had related sense perceptions to Newton's unobservable particles, had been undermined by Berkeley and by Hume's criticism which accepted reality for the sense data only. Thus, the congruence of abstract philosophical cognition and commonsense observation became illusory again. Kant's postulate of the a priori principle of causality and the discoveries of physics and chemistry changed the philosophical concept of the early 19th Century. The disclosures of these sciences, such as the atom theory, the laws of motion and of dynamics, with the corollary theory of cause and effect, could not fail to influence the philosophical conceptions of the time and, in turn, biological investigations which so far had been limited to mere description of facts and their vitalistic interpretation. How deeply Kant's idea of the a priori principle of causality influenced biology may be exemplified by a quotation of Claude Bernard: "The mind of man cannot conceive an effect without a cause, so that the sight of a phenomenon always awakens an idea of causation."

Such historical considerations let one understand the amazing phenomenon of the 25 year old Virchow, just after completion of his medical studies, publishing his conceptual articles in which he set medicine's goal, pathologic physiology through synthesis of dynamic investigation of form and function. In repeated variations he has expressed his belief that disease is life handicapped by various external and internal factors. It is obvious that he realized that exploration of these factors must be one of the important objectives of medical investigation; but the disclosure of cause is not the sole objective. Virchow has also been accused of not appreciating the significance of bacteria in pathogenesis and, by his authority, of blocking the advance of bacteriology. His point of view is well illustrated by his own words: "Parasitic beings, including of course bacteria, are never more than causes; the nature of the disease depends upon the behavior of the organs or tissues with which the bacteria or their metabolic products meet. From my point of view, this distinction is of cardinal importance." I believe that modern microbiology can accept this statement of Virchow as evidence that he was well aware of the importance of bacteria for the study of infectious diseases. But the exploration of etiologic factors is not the ultimate aim of scientific medicine; it is only a means to an end. The ultimate aim is the comprehension of morbid life, and this goal can only be achieved by co-ordinated investigation of the manifestations of disease in the living and the dead, aided by the methods of the exact sciences. In this ideal sense "medicine becomes the science of man, anthropology in its broadest meaning, the highest form of natural science". Medicine of the 19th Century had been built upon this principle and it still inspires the medical science of the present. It is impossible to apportion the shares which the individual sciences have had in the advances of medicine in the past,



although it is evident that today all opinion gives most credit to the contributions of biochemistry. It would be equally unfair to assert that Virchow was the sole architect of the imposing empire of modern medicine, but it may well be said that he was its most articulate prophet. But pathologic anatomy can and must look up to him as the creator of a new science of pathology who led this important branch of medicine from the impasse of mere description to a dynamic interpretation of the dead. The validity of this new concept of interpretation of structural manifestations of disease in terms of vital process is best illustrated if one compares textbooks of pathologic anatomy of the early 19th Century with the compendia of our time. The vague term "cellular degeneration" has been replaced by "disturbance of cellular metabolism" because it has been recognized that the morphological alteration is the result of abnormal chemical and physico-chemical processes within the cell. It must be conceded that the nature of these processes is still obscure and it might be questioned whether we do not simply substitute one term for another one, or in other words, if we do not interpret the ill-defined phenomenon of structural alteration in terms of unknown chemical or physical processes. This criticism seems reasonable, but it can be met, in part at least. When Virchow first observed cell steatosis, he explained the accumulation of fat as the result of a transformation of the cytoplasmic proteins. This was in line with his dynamic approach to morphology, although the answer was wrong. Today we know that the accumulation of lipid substances can be the result of interference with enzymatic processes which result from anoxia, or other factors. While we have to agree to the limitation of our knowledge, we know the problem, and as Virchow said: "The posing of the problem is the first step in scientific investigation." The problems of scientific medicine are the phenomena of disease, be they functional or structural. Pathologic anatomy, since the days of Morgagni, has supplied a vast number of such problems. It could be asked, and indeed it is being asked, whether pathologic anatomy as an observational discipline has not been exhausted and can no more provide investigative medicine with new problems. It seems accepted by some that the morphological manifestations of disease have been fully perceived (Letterer) and that scientific morphology should now devote all its energy to the investigation of the physical and chemical factors responsible for alteration of structure. Parenthetically, it might be said that a similar point of view seems to prevail in the field of clinical investigation, where the pursuit of descriptive phenomenology of disease, the diagnostic art of old-fashioned medicine, has been eclipsed by the introduction of exact physiologic research. In pathologic anatomy this trend of modern times has expressed itself in emphasis upon experimental research. There cannot be a question that alterations of structure characteristic of disease must be investigated with the precise methods of controlled experimentation in order to evaluate the factors responsible for their evolution. But the old-fashioned pathologic anatomist, whose interest still centers in the correct perception of the anatomic lesion in disease, might well be disturbed by certain tendencies in our academic institutions which reveal a disregard for the anatomic foundation of pathology, and a misconception of its role in medicine. He who believes that the advance of medicine can be assured



only if it retains its connection with the past, must show that the basic observational principle of pathologic anatomy can still contribute to the advance of medicine, and that even in recent years observations made at the autopsy table have thrown the first light upon hitherto unknown maladies, or provided basic information which was focussed upon the pathogenetic problem of an obscure disease. I am embarrassed by the abundance, rather than by the scarcity, of material in support of this thesis and would like to present only a few examples. Dorothy Anderson's classical studies of fibrocystic disease of the pancreas demonstrate that even as late as 1939 a new morbid entity could be discovered by exact pathologic anatomic investigation. The recognition of causal relations between environmental factors and the morphology of disease, which Virchow regarded as one of the most significant objectives of pathologic anatomy, cannot be better illustrated than by reference to the work of the man to whom we pay homage tonight. Simple unbiased anatomic observation led Dr. Martland to his far-reaching discovery of the effects of radio-active substances upon the human body, especially the development of bone sarcoma. This disclosure, to paraphrase the words of Aschoff, posed a problem which has engaged biologic and fundamental sciences for years to come. How the almost stubborn insistence that pathologic anatomic investigation can reveal facts of strategic importance for the comprehension of disease might be illustrated by reference to the anatomic studies of systemic lupus erythematosus which have occupied us at The Mount Sinai Hospital for so many years. The unequivocal diagnosis of this puzzling disease has been made possible by studies of exclusively morphologic character, and the observations have posed questions regarding the intercellular substances of the connective tissue which transcend the inquiry of this particular malady into a yet uncharted area of human disease. As a primarily observational discipline, pathologic anatomy has always endeavored to improve upon the methods of perceiving structural alteration in disease. Great advances were made by the steady progress of histopathology, and the heuristic value of a refined technique of micro-anatomy is well illustrated by recent investigations of renal disease. The pioneer work of Jean Oliver with microdissection has clarified a field in which speculation had been rampant because of the ambiguity of clinical and physiologic data and the inadequacy of morphologic comprehension. Most recent investigations of glomerulonephritis (Jones) and other nephropathies (Churg and Grishman) with extremely thin tissue sections have revealed glomerular alterations which throw new light on the morbid process and necessitate a re-investigation of the problem of glomerular structure and function. As so often in the history of medicine, pathology points the way to an understanding of the normal.

These illustrations may suffice to indicate that observational pathologic anatomy is still a powerful tool in the advance of scientific medicine. But our question as to the role of pathologic anatomy in modern medicine must not be limited to its value for the advancement of research. Medicine in the service of humanity must concern itself with the problem of education of the coming generations. I believe it is Utopian to expect that the practice of medicine will soon

mature into an exact systematic scientific activity, and I think medicine in its universal scope is not only applied natural science. Is it not evident that the future physician cannot acquire, within the short period of his schooling, all the factual knowledge which is required for professional competence or for productive scientific achievement? What he must receive is training in unbiased observation and in the ways of scientific thinking. Dr. Griswohl's words about college apply equally well to medical school education: "It is not a quantitative body of memorized knowledge salted away in a card file. It is a taste for knowledge. A taste for philosophy, if you will. A capacity to explore. To question. To perceive relationships between fields of knowledge and experience." It is this equipment which the young physician must acquire in medical school, and it will serve him well in the interpretation of the puzzling manifestations of disease with which he will be confronted in his future practice. This attitude of mind cannot be taught by mere verbalization of facts, but only by the demonstration of intrinsic relationships. To make the chaotic diversity of disease manifestations correspond to a logical system of thought—that is the ultimate aim of medicine. Pathologic anatomy, for nearly two centuries, has developed along these lines. Under the leadership of Morgagni it has brought order into the perplexity of clinical phenomena, by fastening them to the anchor of tangible organic alteration. Under the inspiration of Virchow it has begun to interpret the structural changes as physical or chemical processes accessible to the laws of fundamental science. If ontogenesis is abridged phylogenesis, it may be well that the future physician should develop under the guidance of pathologic anatomy.

# A REPORT ON THE USE OF THE STARCH SPONGE CONE IN PROSTATECTOMY<sup>1</sup>

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The *sine qua non* in prostatic surgery is prompt and effective control of bleeding. The large literature and the variety of devices used in the operating room adequately attests to the difficulty in attaining this goal. Some of the commonly used methods for the control of post-prostatectomy bleeding include gauze packing, rubber dam packing, oxidized cellulose, gelfoam® sponges and various sizes and shapes of hemostatic bag catheters such as the Brake bag, the Pilcher bag, the Foley and Alcock catheters. Packings, with the advantage of effective control of hemorrhage, frequently lead to excessive discomfort to the patient and there is an ever present danger of bleeding at the time of their removal. Oxidized cellulose has been an effective hemostatic agent but often has failed to absorb, causing prolonged convalescence, obstruction, and foreign body formation in the bladder. The gelatin preparations are slippery, difficult to manipulate, and have given inconstant results. Hemostatic catheters are often uncomfortable causing excessive bladder spasms and have proven inconstant in their effectiveness. Perhaps the best hemostasis has been provided by transurethral electro-coagulation post suprapubic prostatectomy followed by a properly placed Foley bag catheter distended to the proper degree. The most recent addition to the armamentarium for local hemostasis is the starch sponge.<sup>2</sup>

The history of the use of starch in surgery started with Scharling (1) who in 1840, first noted the characteristics of frozen starch paste. One hundred years later Bice, McMasters and Hilbert (2) considered the use of starch sponges as vehicles for medicaments. They proposed to incorporate medication in a starch sponge which could be placed into the recesses of a wound with the idea that the medication would be released over a protracted period of time as the sponge was absorbed. Their experimental work demonstrated the fact that the starch was absorbed by the tissues. Correl, Prentiss and Wise (3) one year later investigated absorbable sponges of various materials and demonstrated the total absorption of starch sponges by the body without any demonstrable deleterious effects. Lee and Leiman (4) observed the absorption of starch from the peritoneum without evident inflammation or the formation of adhesions.

In 1949, S. S. Rosenfeld (5) used starch as a hemostatic agent. His experiments were conducted on rabbits, and in fifty-three obstetrical and gynecological cases. In a later report (6) he reiterated his earlier findings and reported the use of the agent in 155 clinical cases. Rosenfeld (5) considered the hemostatic action to be mechanical, i.e. by swelling and compression the flow of blood was arrested. MacDonald (7), however, suggested that the hemostatic action of starch was due

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<sup>2</sup> Solusponge Ritter Prostatectomy Cones, manufactured by the Panray Corporation, 340 Canal Street, New York 13, N. Y.

to the high concentration of sugars found at its surface as a result of enzymatic action. This high concentration of sugars causes agglutination of red cells which implements the clotting of blood.

Ritter and Bloomberg (8) in 1951, reported the first use of starch strips as a hemostatic agent in urologic surgery. They packed these strips into the prostatic fossa following the removal of the adenomata, and noted clear catheter drainage after seventy-two hours. Ritter (8) subsequently suggested that a starch cone, of a suitable shape to fit the fossa be fabricated.

In August, 1953, we were supplied with a starch sponge cone product such as Ritter suggested and we used it in a series of prostatectomies as the major means of hemostasis (Table I). These cases consisted of the following types of prostatectomies: One stage suprapubic prostatectomy with primary closure of the bladder; one stage suprapubic prostatectomy without primary closure of the bladder; second stage prostatectomy; and as an adjunct to fulguration in some cases of retropubic prostatectomy.

In our small series of cases the use of the starch sponge cone was found to give highly satisfactory hemostasis. Because of this fact, and being fully cognizant of the limitations of conclusions based on the small series, we are presenting this report in order that the starch cone may receive widespread usage and evaluation.

#### DETAILS OF TECHNIQUE WITH THE STARCH CONE

The details of the technique that has been used will now be considered. All the equipment and materials should be assembled, tested, and ready before surgery is actually started. There should be as little delay as possible between the enucleation of the prostate and the insertion of the cone. This is an extremely essential point and is crucial to the success of the procedure.

We shall first consider a suprapubic prostatectomy without primary closure of the bladder. A transverse suprapubic incision is used in preference to the longitudinal incision because of the infrequency of post-operative hernia in the former. The bladder is exposed and the anterior wall of the bladder mobilized. Two chromic guide sutures are placed in the previously distended bladder which is then opened between them by means of a transverse incision. The incision is made larger than usual so that subsequently the starch cone can be easily inserted. The prostate is then digitally enucleated in the usual fashion using digital counter pressure through the rectum. Immediately following the removal of the adenoma a temporary warm, moist packing is inserted into the fossa and left in place until the catheter and starch cone have been prepared. A 22 French, 30 cc balloon catheter is mounted on an introducer and passed through the urethra into the bladder where its tip is grasped and pulled out through the incision. The starch cone is threaded over the catheter, apex downwards, to a point below the bag. The size of the cone utilized, either 20cc, 45cc, or 75cc is judged by an estimate of the size of the prostatic fossa. The cone should be smaller than the prostatic fossa so that the fossa can contract around it, and so that it may swell within the fossa. The balloon is then distended sufficiently to prevent the tip of the catheter slipping into the fossa which may impede subsequent drainage when



TABLE I  
*Summary of cases*

AGE	BLOOD PRESSURE	GLAND WEIGHT	DIAGNOSIS	OPERATIVE TECHNIQUE
1. 67	—	48 gms.	Benign prostatic hypertrophy	II stage suprapubic
2. 71	120/65	53 gms.	Benign prostatic hypertrophy	I stage suprapubic
3. 66	140/80	110 gms.	Benign prostatic hypertrophy	I stage suprapubic
4. 64	145/85	90 gms.	Benign prostatic hypertrophy	I stage suprapubic
5. 70	130/66	50 gms.	Benign prostatic hypertrophy	II stage suprapubic
6. 84	162/78	90 gms.	Benign prostatic hypertrophy	II stage suprapubic
7. 67	150/100	98 gms.	Benign prostatic hypertrophy	I stage suprapubic
8. 69	160/100	45 gms.	Benign prostatic hypertrophy	I stage suprapubic
9. 62	130/80	50 gms.	Benign prostatic hypertrophy	II stage suprapubic
10. 78	140/70	66 gms.	Benign prostatic hypertrophy	II stage suprapubic
11. 53	160/80	43 gms.	Benign prostatic hypertrophy	II stage suprapubic
12. 69	124/80	87 gms.	Benign prostatic hypertrophy	II stage suprapubic
13. 63	142/96	93 gms.	Benign prostatic hypertrophy	I stage suprapubic
14. 78	180/104	48 gms.	Benign prostatic hypertrophy	II stage suprapubic
15. 73	110/64	85 gms.	Benign prostatic hypertrophy	I stage suprapubic
16. 65	164/80	62 gms.	Benign prostatic hypertrophy	Retropubic
17. 65	140/70	45 gms.	Benign prostatic hypertrophy	I stage suprapubic
18. 52	136/84	40 gms.	Benign prostatic hypertrophy	Retropubic
19. 68	140/70	53 gms.	Benign prostatic hypertrophy	Retropubic
20. 73	146/66	63 gms.	Benign prostatic hypertrophy	Retropubic
21. 68	170/110	35 gms.	Benign prostatic hypertrophy	II stage suprapubic
22. 73	168/98	90 gms.	Benign prostatic hypertrophy	I stage suprapubic
23. 77	140/88	34 gms.	Benign prostatic hypertrophy	I stage suprapubic
24. 66	150/85	50 gms.	Benign prostatic hypertrophy	II stage suprapubic
25. 76	150/60	10 gms.	Benign prostatic hypertrophy	I stage suprapubic
26. 67	130/70	60 gms.	Benign prostatic hypertrophy	II stage suprapubic
27. 65	130/60	30 gms.	Benign prostatic hypertrophy	I stage suprapubic
28. 57	142/66	41 gms.	Benign prostatic hypertrophy	Retropubic
29. 61	140/80	5 gms.	Benign prostatic hypertrophy	I stage suprapubic
30. 62	180/80	40 gms.	Benign prostatic hypertrophy	I stage suprapubic
31. 66	200/90	103 gms.	Benign prostatic hypertrophy	II stage suprapubic
32. 70	154/86	100 gms.	Benign prostatic hypertrophy	I stage suprapubic
33. 62	165/90	35 gms.	Benign prostatic hypertrophy	I stage suprapubic
34. 65	170/96	40 gms.	Benign prostatic hypertrophy	II stage suprapubic
35. 79	170/70	100 gms.	Benign prostatic hypertrophy	II stage suprapubic
36. 60	150/90	45 gms.	Benign prostatic hypertrophy	I stage suprapubic
37. 67	150/90	45 gms.	Benign prostatic hypertrophy	I stage suprapubic
38. 61	100/84	35 gms.	Benign prostatic hypertrophy	I stage suprapubic

the suprapubic tube has been removed. The wound is spread apart and the cone is *placed* into the prostatic fossa and *gently* molded into place using the rectal fingers at the same time. The bag of the Foley catheter is now gently brought down so that it contacts the upper surface of the cone. A suprapubic tube is inserted into the bladder and immediate irrigation via the catheter is commenced. In about one minute the irrigation fluid will become clear or slightly pink. The bladder is closed around the suprapubic tube. A Penrose drain is inserted to the space of Retzius and one to the peritoneum and the wound is closed in layers



in the usual manner. Through and through irrigation is continued with sterile water for twenty-four to thirty-six hours.

The technique for a second stage suprapubic prostatectomy is obviously similar. At this point we would like to describe the procedure of a one stage suprapubic prostatectomy with primary closure of the bladder. The technique is similar to the above-described procedure except that a three-way Aleock catheter is used in the bladder and threaded through the starch cone. The irrigation is performed while the edges of the bladder incision are temporarily approximated by crossing the guide sutures. When irrigation shows that hemostasis has been achieved, the bladder incision is closed by a continuous chromic suture followed by a second layer of interrupted chromic sutures. Penrose drains are placed as mentioned above. Most cases are quite clear when they leave the operating room. Continuous irrigation through the Aleock catheter is maintained for twenty-four to forty-eight hours. The drainage tends to be pink for several hours after the patient is returned to the ward. With this closed technique more careful observation and attention is required because of the formation of tiny blood clots which can block the outflow of the catheter. With an observant nurse, however, and a Toomey syringe, this occasional occurrence can be promptly handled.

We have used the starch sponge cone in doing retropubic prostatectomy. The cone is inserted into the fossa in a similar fashion to that described, and the prostatic capsule is closed over it. In these cases we have found the 20cc cone to be usually the most suitable, and fulguration of active bleeding points is, of course, first carried out.

Following the above procedures the catheter is usually strapped to the thigh but only under the slightest traction. This is done simply to keep the catheter and the cone in the original position if the patient reacts or moves about excessively during the immediate post-operative period.

#### SUMMARY AND CONCLUSIONS

A technique for the use of the starch sponge cone as the primary hemostatic agent in both suprapubic and retropubic prostatectomy together with a small series of cases in which it has been used satisfactorily is presented. The literature has been briefly surveyed. It is felt that this is more effective and advantageous than hitherto applied methods.

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PATHOGENESIS OF ARTERIOSCLEROSIS<sup>1</sup>

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The generic term "arteriosclerosis" demands definition because for reasons I have previously submitted (1) I do not consider the term synonymous with "atherosclerosis." This is why I have added the prefix "hyperplastic." By hyperplastic arteriosclerosis I refer to a consistent hyperplasia of the intima and elastica in contrast to atherosclerosis which represents a deposit of lipoid within the walls. The two may be entirely independent and when associated, hyperplastic arteriosclerosis comes early and atherosclerosis later. No study of arteriosclerosis can be entirely valid unless this differentiation is acknowledged. Furthermore, it is necessary to view the problem not from the static but from the dynamic point of view, namely, the observation of arteriosclerosis from birth to old age. Classification will be further clarified by a study of arteriosclerosis not only in different portions of the arterial tree, but also of morphologically comparable lesions in other sectors of the vascular system, namely, the chambers of the heart, the veins and the capillaries. Only too frequently a part of the general morphogenesis of arteriosclerosis is emphasized to the exclusion of the whole.

While there are many aspects of the problem of arteriosclerosis that await solution, there are certain common denominators upon which most are agreed. 1. Hyperplastic arteriosclerosis is not limited to the human race but affects all animals that possess a vascular system such as our own and who live long enough; 2. In the anatomical sense no adult human being is exempt. If we view the progressive thickening of the intima and the hyperplasia of the elastica which begins soon after birth as the earliest lesion, hyperplastic arteriosclerosis is omnipresent in mankind, except in suckling infants. There is ample testimony that no race is free from arteriosclerosis. It has been found in post mortem examination of negroes in Africa (2) in the Eskimo (3) and in Orientals (4). Furthermore, it has been found in antiquity, as autopsies on Egyptian mummies attest (5); 3. Other things being equal, age has a direct bearing upon both the incidence and intensity of arteriosclerosis. Gross arteriosclerosis of the systemic circulation is notoriously absent at birth. It becomes grossly visible approximately in late adolescence and becomes more widespread and more intense in the declining years (6). This applies not only to man but to animals whose life tenure is not too short (7); 4. Simultaneous observations on the incidence of gross arteriosclerosis of the vessels of both the greater and pulmonary circulation show that these are entirely independent. In other words, arteriosclerosis of the aorta may be conspicuous while the pulmonary artery is free and vice versa. Gross arteriosclerosis affecting both the aorta and the pulmonary artery simul-

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taneously is the exception rather than the rule, and in the post mortem material in the past 25 years at The Mount Sinai Hospital, the incidence is only about 6 per cent. The lesion may be more prominent in one segment than in others but by and large when the aorta or the main pulmonary trunk is affected the corresponding terminal branches are likewise affected, and the converse is also true. Since we have no reason to suspect a difference in tissue susceptibility between the systemic and pulmonary vasculature, this difference in incidence of hyperplastic arteriosclerosis between the systemic circulation and pulmonary artery is deeply significant since it forthwith excludes any toxin, metabolic product, infection or a general malady such as diabetes mellitus as a cause of hyperplastic arteriosclerosis, because the same blood bathes both circulations.

What then is the common factor that can integrate these fundamental principles? It must possess the attributes of universality, of time, and of place. In other words it must be a continuously acting and dynamic element and part of the normal workings of the organism. Moreover, it must be an agent that accounts for the independence in incidence of hyperplastic arteriosclerosis in the greater circulation and in the pulmonary artery. The only factor that meets these specifications is the normal systemic intra-arterial pressure. Under what circumstances does arteriosclerosis of the pulmonary artery arise? In 1. emphysema; 2. mitral disease; 3. obliterative lesions of the lung that destroy a large part of the capillary bed; 4. prolonged congestive failure; 5. open ductus arteriosus or other communications between the two sides of the heart when the shunt is from left to right. The common factor in all these conditions is an increase in the pressure within the pulmonary artery. With cardiac catheterization (8) this has been demonstrated. The mechanism whereby these lesions produce hypertension of the pulmonary circuit has been described by Wiggers (9). Now, inasmuch as the normal pressure in the pulmonary artery is only one sixth that in the aorta, and sustained hypertension of the pulmonary circulation does not nearly approach that in the aorta, it is safe to conclude that normal arterial pressure may produce arteriosclerosis, if given sufficient time. A "primary" arteriosclerosis of the pulmonary artery has often been invoked but there is a question whether such reported cases are valid. Either the protocol is incomplete, or a cause for the hypertension of the pulmonary circulation is ignored, such as congestive failure, emphysema, bronchiectasis, etc. This applies particularly to the reported cases of "Ayerza's disease." In others, a thromboarteritis of the pulmonary artery is described. In The Mount Sinai Hospital, thus far, no well screened case of primary pulmonary arteriosclerosis has come to light. But there are many other evidences that the normal intra-arterial pressure is the most important causative factor in hyperplastic arteriosclerosis. 1. When hypertension is superimposed, the age limit for the production of arteriosclerosis is lowered and the lesions are intensified. This accounts for all instances of juvenile arteriosclerosis. Except with a previous or present hypertension, juvenile arteriosclerosis, as far as we are aware, does not occur. On the other hand, juvenile arteriosclerosis of the pulmonary artery is common enough

in hypertension of the pulmonary artery caused by mitral disease, for instance. It has been reported even in suckling infants with congenital heart disease (10, 11). It is sometimes forgotten that systemic hypertension is a hyperkinetic disease and is not a new insult that has invaded the organism, but an increase of a normal function. It has been shown that, morphologically speaking, the arterial lesions accompanying hypertensive disease differ in no way from that observed in normotensive individuals, except in degree (12). 2. Hypotension, on the other hand, decreases the incidence and the intensity of arteriosclerosis. In active tuberculosis, especially with emaciation, where blood pressures are notoriously low, arteriosclerosis is less common, age for age (13, 14). In mass statistics, Hunter (15) has shown that the incidence of cardiovascular disease is appreciably less in hypotensive persons. 3. The effect of intravascular pressure is exemplified in the intensification of the process at points in the vascular channels where the pressure is exerted against a resistance; A. Near the origin of the intercostal arteries which fix the posterior wall of the aorta; B. In the abdominal aorta which is fixed to the rigid vertebral column; C. The anterior aspect of the aorta is much less involved than the posterior; D. Arteriosclerosis is more pronounced in that part of the circumference of the dural vessels that is imbedded in the bony framework (16); E. Westenholfer (17) showed that the patches of arteriosclerosis are more apt to occur in those portions of the aorta that lie against the ridges of the vertebrae than in the hollows; F. Arteriosclerosis of the pulmonary artery is more prominent in those areas that lie against the rigid bronchus; G. The reason why the left coronary artery is more frequently and severely affected than the right is, we believe, because it is imbedded in a thicker wall than the right and is subjected to greater tensions during systole. Dock (40) found that the intimal thickening of the left coronary artery was two and a half times thicker in males than in females, thereby accounting for the greater incidence of coronary disease in males. Furthermore, the patches are more numerous and prominent on the portion adjacent to the muscle; H. In perforation of the ventricular septum a patch of sclerotic endocardium is found in the ventricular wall opposite the perforation. Not only are the hyperplastic changes most prominent at these sites, but, as we shall elaborate subsequently, the deposition of lipid as well. These observations help explain some of the apparently haphazard localizations of the patches in the arterial tree. Apparently, therefore, the incidence and location of arteriosclerotic patches are conditioned not only by the intra-arterial pressure but also by the external resistance. This may help to explain why the arteries of the mesentery are notoriously free from gross arteriosclerosis, since they are mostly surrounded by the gas containing gut; 4. The effect of pressure upon the development of sclerosis of the intima and elastica is well exemplified by the analogous lesion in the veins, namely in phleboscclerosis. This is particularly impressive because under normal circumstances, the pressure in the veins hovers around zero mm. of mercury, and when venous pressure rises, as for instance in congestive failure or constrictive pericardium, it never even approximates the normal systemic



arterial pressure. Furthermore, patients with prolonged venous hypertension do not as a rule live very long. Phlebosclerosis just as hyperplastic arteriosclerosis is characterized by a pronounced thickening of the intima and to a lesser degree of the elastica; lipid deposition is extremely rare (18). In contrast to the arteries, the veins even in the aged are normally devoid of an intima. I have examined the vena cava, for instance, in many individuals of the seventh and eighth decades and unless prolonged congestive failure occurred, the endothelium lies directly against the elastica interna as in the newborn. Pathogenetically, phlebosclerosis occurs only in venous hypertension; A. In long standing varicosities of the lower extremities; B. Carrel (19) demonstrated that sclerosis occurs in a vein situated between the divided ends of an artery. This is significant because every factor except increased pressure can be excluded and it may therefore be viewed as compensatory; C. Phlebosclerosis is found in the venous segment of an arteriovenous aneurism (20); D. The Cramer-Shilling lesion (21). This is a patch of sclerosis on the lowest portion of the inferior vena cava on the posterior wall exactly at the site where the two currents from the common iliaes meet; this area also lies against the comparatively rigid aorta. This occurs almost normally in all individuals past the age of 55; E. Sclerosis of the portal vein is found in a very high percentage of cases of portal cirrhosis which induces portal hypertension (22); F. Phlebosclerosis of the hepatic vein is common in prolonged hypertension of the pulmonary artery. The back pressure is transmitted downward into the inferior cava and thence to the hepatic veins. It is always associated with cardiac cirrhosis (23). These various examples of phlebosclerosis comprise all the recorded instances of true phlebosclerosis. Obviously, we do not include the sclerosis consequent to infections, syphilis, etc. These have an entirely different morphology and pathogenesis. It is safe to conclude, therefore, that phlebosclerosis, as manifested by thickening of the intima and hyperplasia of the elastica, is always the result of venous hypertension.

*The biology of hyperplastic arteriosclerosis.* If intravascular pressure is a causative factor in hyperplastic arteriosclerosis, it becomes obvious that hyperplastic arteriosclerosis in the anatomical sense must begin at birth. Clinically its deleterious effects become apparent in the declining years but clinical and anatomical arteriosclerosis are fortunately not always coexistent. In contradistinction to other organs the arteries do not retain their finer anatomical characters from birth to old age but undergo a slow but progressive change. At birth the intima is hardly visible, so that the endothelium lies directly upon the elastica interna which is a single layer. Already in the first year a distinct collagenous intima becomes visible (24, 25) and this becomes progressively wider with advancing years. Table I taken from Schafer's Histology (26) shows the measurements of the intima at different ages. In old age the thickened collagenous intima frequently undergoes hyaline change. Reduplication of the internal elastic layer also begins as early as the second year in the larger arteries and involves the smaller vessels after middle life (27). This hyperplasia is also progressive with the years. The infiltration with lipid is a comparatively late phenomenon. These two processes, the progressive thickening of the intima and the hyper-



TABLE I

AGE	INTIMA
	(microns)
Birth . . . . .	6
10 years . . . . .	54
35 years . . . . .	124
50 years . . . . .	181
70 years . . . . .	190

plasia of the elastica differ in intensity whether the artery is of the elastic or the muscular type but they are never absent in the course of growth.

Viewed biologically therefore hyperplastic arteriosclerosis represents the maturation of a normal evolutionary process, and this explains the difficulty many observers have had in determining where physiological ageing ends and disease begins. For instance, Brenner (28) reports an incidence of 80 per cent of arteriosclerosis of the pulmonary artery, his criterion being the microscopic thickening of the intima of the larger and smaller branches. Practically speaking, the only normal pulmonary arteries in his observations occurred in infants. Anatomically, Brenner is perfectly correct. Clinically his report is misleading.

The hyperplasia of the intima and elastica bears all the earmarks of a compensatory process and may be viewed as an adaptation to the progressive rise of intra-arterial pressure that normally proceeds from birth to old age or if there is no perceptible increase, to the prolonged maintenance of the normal pressures. When hypertension supervenes the process comes earlier and is intensified. In the form of an equation, therefore, hyperplastic arteriosclerosis = intravascular pressure  $\times$  time. Apparently Thoma's (29) third law of growth of vessels, namely that the thickness of the vessel wall is dependent on the difference between the intravascular and extravascular pressures, which he applied to the embryonal development of arteries, is perfectly applicable to post-embryonal growth as well.

Thus far, I have emphasized the hyperplastic lesions of arteriosclerosis, since I consider them primary. This leads to a discussion of the more conspicuous and potentially dangerous secondary lesions of arteriosclerosis, namely atherosclerosis.

I use the term hyperplastic arteriosclerosis because it embraces the fundamental pathogenetic mechanisms in the course of a biological progression from birth to old age. In this sense it is irreversible. This view has been challenged in some quarters where arteriosclerosis is viewed as synonymous with atherosclerosis. There is no doubt that in experimental atherosclerosis and sometimes even in man atherosclerosis is reversible. Nevertheless, there is every evidence that while atherosclerosis may be an independent phenomenon, it represents only a facultative part of the general morbid process comprised under the rubric arteriosclerosis. The most convincing proofs of this is shown in observations of arteriosclerosis of the pulmonary artery. Arteriosclerosis of the pulmonary artery in its early stages is characterized by intimal collagenous hyperplasia

sometimes of enormous degree together with hyperplasia of the elastica interna. Lipoid deposition is conspicuously absent and found only in cases of prolonged hypertension of the pulmonary circulation. Wilens (30) believes that intimal thickenings in the aorta are secondary and represent resultants from atherosclerotic deposits since they occur at sites where in experimental atherosclerosis the lipid is absorbed, but the fact that reverse relationships exist in the pulmonary artery is a valid argument that the same sequence of events occurs in all arteries. Furthermore, intimal thickening beginning at birth is a normal involutionary process and is not preceded by lipid deposition. In a study of the histogenesis of coronary arteriosclerosis, Moon and Rinehart (31) showed that the thickening of the intima preceded the deposition of lipid. Furthermore, they maintain that the fibrous plaques secondary to those derived by inducing experimental hypercholesterolemia bore little resemblance to the histogenesis of coronary arteriosclerosis encountered in man. These evidences again reveal the lack of true perspective when observations are confined to studies on the aorta alone.

There is no doubt that atherosclerosis may be an independent lesion. This is manifest in experimental atherosclerosis. In such circumstances, it may also be reversible, in the sense that the lipid may be completely absorbed, even though local intimal thickenings persist (32). In man, intimal microscopic deposits of lipid begin at birth and increase with each decade (33). Table II, taken from Lober (33) shows the incidence in the coronary artery.

Zinserling (34) found such deposits frequently from the sixth month and these were practically constant after the fourth year, becoming more marked with advancing age. According to Aschoff (35) visible lipid deposits are common in the root of the aorta and especially in the aortic leaflet of the mitral valve in the suckling infant when the nourishment is rich in lipoids; they become absorbed in the weaning period to become visible again at puberty, after which they become progressively conspicuous with advancing years; apparently between the periods of weaning and adolescence atherosclerosis is a reversible process.

TABLE II

YEAR	DEGREE OF ATHEROCLEROSIS		
	Males	Females	Combination
N B to 1 mo.	1.4	1.4	1.4
1-12 mo.	2.6	2.4	2.4
1-9 yr.	3.1	3.0	3.0
10-19 yr.	5.0	4.3	4.3
20-29 yr.	5.6	4.9	4.9
30-39 yr.	7.6	7.1	7.1
40-49 yr.	8.8	8.0	8.0
50-59 yr.	9.5	8.8	8.8
60-69 yr.	10.4	9.9	9.9
70-89 yr.	10.8	10.6	10.6

Taken from Lober.

After this the rate and amount of deposition of lipoid are influenced by various factors, but there is grave doubt whether it may become completely reversible, since one or more factors that contributed to the deposition cannot be eliminated, such as the normal cholesterol content of the blood, intravascular pressure and the effect of ageing on the ground substance. These I shall discuss more fully shortly. While there is no doubt that atherosclerosis contributes greatly to the destructive effects of vascular disease, especially in the coronary system, by narrowing, thrombus formation, rupture of an atheromatous abscess, or intramural hemorrhage (36) one cannot ignore the hyperplasia of the intima and the elastica as equally important factors. This is strikingly illustrated in the strangling effects on the blood supply by arteriolosclerosis in which the hyperplastic changes are by far dominant. In addition they contribute to a weakening of the vascular wall making it more susceptible to rupture.

The production of experimental atherosclerosis and its potential reversibility has conferred a more rosy aspect to the problem of arteriosclerosis and is responsible for the present activity in this field.

The only experimental method that simulates the human variety of arteriosclerosis is the cholesterol feeding method initiated by Anitschkow and Chalатов (37). It was soon recognized that there were serious morphological differences between the human and experimental variety, especially in the lack of the selective distribution in the arterial tree, in the fact that it was produced by unphysiological means and only in herbivora. Since then some of these differences have been eliminated. For instance, in the chick the deposition resembles more the topography of spontaneous arteriosclerosis in man (38). Anitschkow (32) produced atherosclerosis in rabbits without the induction of a severe hypercholesterolemia by feeding smaller amounts of cholesterol over a more prolonged period. Katz and Stammler (38) did likewise with the chick. Finally Steiner and Kendall (39) have produced atherosclerosis in dogs with the combined administration of cholesterol and thiouracil. Nevertheless critically examined the accumulated evidence shows that what has been accomplished is the atherosclerotic moiety of arteriosclerosis. In other words only a part, and indeed an important part of the lesions of arteriosclerosis has been reproduced. I have no intention of underemphasizing the importance of the atherosclerotic element, but I maintain for the sake of a correct perspective that the two processes be not confused. Hyperplastic arteriosclerosis may exist alone; atherosclerosis may exist alone; usually the two are associated especially in adult life. The problem now veers to another phase. Why does atherosclerosis occur spontaneously in man with normal cholesterol blood values? There are human disorders associated with hypercholesterolemia that lead to early gross atherosclerosis, such as essential or familial hypercholesterolemia, the nephrotic syndrome, hypothyroidism and prolonged biliary obstruction, but these comprise but a fraction of the totality of human vascular disease. This phase of the problem has evoked the most lively interest in the last few years. The problem was attacked in a number of ways. It was soon found that even in experimental arteriosclerosis there was no direct linear relationship between the degree of hypercholesterolemia

and atherosclerosis. In rabbits according to Dock (40) deposition of lipid is apparent at a blood level of 100 mgm. per cent, while in dogs it occurs at a level of 400 mgm. per cent. In alloxan diabetes the blood cholesterol may attain a level of even 1000 mgm. per cent and not only is atherosclerosis not produced, but the animal does not even develop atherosclerosis when it is fed cholesterol (44). The same occurs when the rabbits are given detergents, such as Tween 80 (42). In man also, it was soon apparent that the development of atherosclerosis did not always hold a linear relationship to the blood level of the cholesterol but that it sometimes depends upon the ratio of cholesterol to the phospholipid in the plasma. Barr and his coworkers (43) employing one of the fractionation methods of Edwin Colm have studied not only the total cholesterol and the phospholipid cholesterol ratio but also the distribution of the alpha and beta lipoproteins in the plasma in different animals, in infants, young men and women and in human conditions associated with atherosclerosis. They particularly emphasize the significance of the distribution of the alpha and beta lipoproteins since "such changes are apparent without hypercholesterolemia or a recognizably significant elevation of the cholesterol phospholipid ratio." Their figures showed deviations from normal patterns that bear a relation to the predisposition to atherosclerosis. Barr's observations (43) bear promise for future investigation, but he admits that the range is too wide to permit the employment of these factors as a diagnostic measure.

Gofman's (44) observations introduced a new slant into the problem. Briefly he found with the ultracentrifuge that the molecules designated by the label Sf 10-20 bear a remarkable relation to the incidence of atherosclerosis. Patients with coronary infarction and diseases predisposing to atherosclerosis show a higher incidence of these molecules than presumably normal individuals. These molecules are also elevated in essential hypercholesterolemia, xanthomatous diabetes with vascular disease, in the nephrotic syndrome, in hypothyroidism and in cholesterol fed rabbits.

Gofman's studies (44) and those of Barr (43) while highly suggestive have the same defect namely, that their findings bear only an approximate and not an absolute relation to the incidence of atherosclerosis. Unexplainable inconsistencies have been found with both methods. Furthermore, their results have been applied to individuals who have already developed vascular disease, usually myocardial infarction. We anticipate with much interest studies which will show whether their findings are congenital or acquired, and if acquired when and how the change occurs and whether they change over the years.

It is apparent that from the physical and chemical aspects, the precise relation of the plasma lipids, with or without combinations with proteins, remains illusive.

There is strong evidence that most of the lipid in atherosclerosis comes by imbibition from the plasma. This deduction is based upon the following observations. 1. There is a striking similarity in the chemical composition and distribution of the lipoids in the plasma and in the arterial wall (45); 2. In experimental atherosclerosis the initial deposit is in the intima; 3. There is an increase in the amount of lipid in hypertensive states, whether of the greater or of the lesser circulations. Conversely in hypotension atherosclerosis is less intense (15);



4. Anitschkow (32) showed that the lipid was deposited in the same areas that revealed the greatest permeability to colloidal dyes such as trypan blue; 5. In hypercholesterolemic states the deposits are greater than in normocholesterolemic; 6. Wilens (46) introduced serum into excised common and external iliac arteries and after 18 hours at pressure of 200–300 mm. mercury he found lipid in the intima. In 36 to 48 hours the entire intimal surface was impregnated. At physiological pressures, that is between 75 and 125 mm. mercury, scanty lipid was found at the end of 24 hours. Evans and his co-workers' (47) results were similar.

Inasmuch as the plasma lipid exists in a colloidal form and that in the artery as granular deposits, it is presumed that the intima takes an active part in this transformation.

Not all of the lipid enters the vessel wall by imbibition. Winternitz and his coworkers (48) have to my mind adduced convincing evidence that some lipid is the result of hemorrhages from the rupture of the intimal capillaries.

Another factor in the production of atherosclerosis that necessitates serious consideration is change in the vessel wall, especially the ground substance, that enhance the penetration and localization of the lipid. It would be difficult to prove that lipid can penetrate the walls of a normal vessel, especially in man, since the intima and elastica begin to change morphologically soon after birth. Many years ago Aschoff (49) postulated that age itself could change the ground substance. Katz and his coworkers (50) demonstrated experimental atherosclerosis in cockerels only five weeks old. It is conceivable that a structure such as an artery which is continuously battered by mechanical stresses must in the course of years change structurally. I have already referred to the thickening of the intima and the reduplication of the elastica which may be viewed as compensatory phenomena. Dock (40) believed that the early thickening of the intima of the coronary artery was the precursor of atherosclerosis. In a study of the histogenesis of coronary arteriosclerosis, Moon and Rinehart (31) showed that the earliest lesion is represented by a thickening of the intima. Later several histological changes seem to occur spontaneously. 1. An increase in the amount of ground substance; 2. The proliferation of subendothelial fibroblasts; 3. Small areas of degeneration of the intimal elastic membrane. Lipid was sometimes but not consistently present in early lesions. In later lesions the above changes were exaggerated and lipid was always present.

In addition a metachromatic substance consisting of mucopolysaccharides is deposited in the vessel wall (51–55). This deposit is already visible in children (55) and increases with age (52–54). Many observers believe that the mucopolysaccharides act as precursors for the deposition of lipid in the vessel wall. There is abundant testimony that injury of the vessel wall may intensify the deposition of lipid, for instance, by syphilis. Ever since Anitschkow (32) who maintained that lipid is deposited only in injured vascular areas, numerous observers have produced experimentally a localized atherosclerosis by injury of the vessel wall, for instance by cauterization (56, 57) adrenalin (32) detergents (58) and most recently by the induction of scurvy (59).

That intravascular pressure is a vital factor in the production of athero-



sclerosis cannot be gainsaid. I have already cited the increase in atherosclerosis induced by hypertensive states as confirming the mechanism of imbibition of lipid through the vascular wall. As corroborative evidence of the importance of intravascular pressure, I cite again the profound difference in incidence of atherosclerosis between the lesser and greater circulation and the almost complete absence of atherosclerosis in the veins. Faber (60) showed that experimental atherosclerosis can be produced even with a normal blood cholesterol provided hypertension is induced.

Finally, there is the dynamic factor of time. Anitschkow (32) recognized this when he showed that atherosclerosis can be produced with a lesser degree of hypercholesterolemia if the experiment is prolonged over a longer period. The time factor is probably one of the considerations that enters into the species difference of spontaneous arteriosclerosis, since by and large, the longest lived animals in terms of their period of captivity, showed arteriosclerosis (7). The greatest incidence of arteriosclerosis is in birds who are notoriously long lived. The close relation of arteriosclerosis and atherosclerosis to senescence is certainly true in man. The time factor may be one of the reasons, aside from a distinctive lipid metabolism, why rats, who are the shortest lived mammal, averaging only about three years, are remarkably free not only from spontaneous but also from experimental atherosclerosis.

Certainly in every field except experimental arteriosclerosis, in pulmonary hypertension and in juvenile hypertension of the greater circulation, arteriosclerosis is a senescent phenomenon.

It is obvious from the various factors that I have enumerated that no inclusive theory of atherosclerosis is applicable. It is in the interaction of all these factors, the quantity of lipid, the physical and chemical nature of the blood lipids, changes in the ground substance and intravascular and extravascular pressure changes, that atherosclerosis is reproducible and then only if given sufficient time. For instance, it will take a longer period to produce atherosclerosis with a normal plasma cholesterol than with a hypercholesterolemia, and it will require a shorter period with hypertension. In the pulmonary circulation, atherosclerosis exceptionally occurs and only with pulmonary hypertension because the normal pressure is only between 15 and 25 mm. mercury. In the veins atherosclerosis practically never occurs because the pressure is too low no matter how long the individual lives. Statistical studies on the incidence of atherosclerosis in various sections of the vascular tree are valueless unless the time factor is considered. The entire problem of atherosclerosis must be viewed dynamically as well as statically.

#### SUMMARY

Evidence is submitted that intravascular pressure is the most important conditioning factor in the production of hyperplastic arteriosclerosis. In this concept, hyperplastic arteriosclerosis begins at birth and proceeds unremittingly into old age. Histologically it is impossible to decide therefore when normal ageing ends and disease begins. The transition from a microscopic process to

one that becomes visible to the naked eye comes in late adolescence for it is then that the secondary deposition of lipoid gives gross visibility. Anatomical arteriosclerosis and clinical arteriosclerosis are by no means synonymous. Evidence has been submitted that atherosclerosis is not the primary but a secondary phenomenon and that it is the resultant of the interaction of numerous factors, the most important being the chemical and physical properties of the plasma lipid, changes in the ground substance, the intravascular pressure and the dynamic effect of time.

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## CHYLOTHORAX<sup>1</sup>

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The increasing frequency of chylothorax, and the development of new methods of management, both conservative and surgical, contribute to the importance of understanding this condition. The rational management of a particular case depends not only on a knowledge of the clinical picture, but also on a thorough understanding of the anatomical and physiological aspects of the problem. It is the purpose of this communication to present and to discuss the more significant features of this condition, as well as the problems of therapy.

Our recent experience with a case which was followed with careful studies illustrates many of the problems in handling this condition.

### CASE REPORT

J. G., a 30 year old Puerto Rican male was admitted to The Mount Sinai Hospital on September 6th, 1952, one-half hour after being stabbed in the chest. Thirty minutes before admission to the hospital, while in a scuffle, the patient was stabbed in the left anterior chest with a knife. On admission he complained of generalized pain over the left chest accentuated by respiration, but denied dyspnea, abdominal pain, nausea or vomiting. His past history was entirely negative for previous illnesses, injury or surgery.

Physical examination disclosed a thin but well-developed male with blood oozing from a chest wound. His temperature was 99.2°F., pulse 80, respirations 18, and blood pressure 110/80. Examination of the head and neck revealed no abnormalities. There was an oozing, clean, stab wound about 1" in length located at a point one-half inch to the left of the midline at the level of the junction of the sternum and the xiphoid. Both sides of the chest expanded fully on respiration, and the lungs were clear to percussion and auscultation. The PMI was in the 5th left intercostal space at the midclavicular line, and there was no evident shift of the heart. The heart sounds were of good quality, the rhythm was regular and no murmurs were heard. The remainder of the physical examination was entirely negative. The laboratory study revealed a normal blood count and urinalysis. Chest x-ray and fluoroscopy were normal at the time of admission. There was no evidence of pneumothorax, pleural effusion, nor of free air in the peritoneal cavity.

The stab wound was closed and the patient was carefully observed for a period of three days for evidence of any complications, and was discharged asymptomatic on the fourth hospital day.

The next day, the patient again presented himself for admission with the history that several hours after discharge he began to notice the onset of mild

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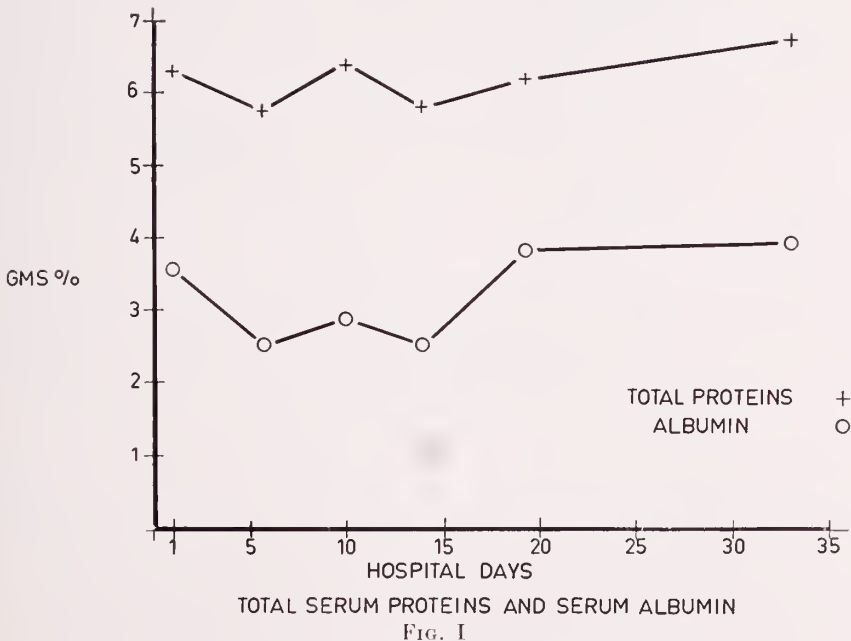
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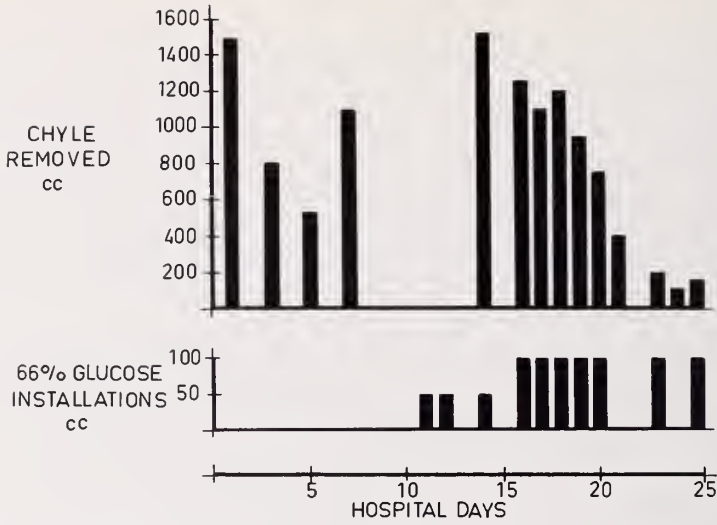


dyspnea. This rapidly progressed and at the time of readmission had become quite severe. There were no other symptoms. Physical examination revealed the patient to be in marked respiratory distress, with evidence of a large pleural effusion extending to the fourth intercostal space on the right. These findings were confirmed by radiological examination. The remainder of the examination was essentially unchanged. Thoracentesis of the right pleural cavity was performed and 1560 cc. of creamy, light pink fluid was obtained. This procedure caused marked relief of the patient's dyspnea. The pleural fluid was identified as chyle by the addition of Sudan III. Large orange-stained fat globules were found in great numbers on microscopic examination.

The patient was permitted nothing by mouth for the first four days and then was placed on a high protein, high carbohydrate and low fat diet. This was done to insure a sufficient caloric intake, and at the same time reduce the quantity of chyle by maintaining his intestinal absorption of fat at a minimum. Considerable emphasis was placed on maintaining a positive nitrogen balance. This was achieved by the additional administration of supplemental feedings of a protein hydrolysate in milk, whole blood, and intravenous infusions of salt-free albumin, totalling 450 gm. in 23 days. Figure I demonstrates the effectiveness of these measures in keeping the patient's serum protein and albumin at adequate levels.

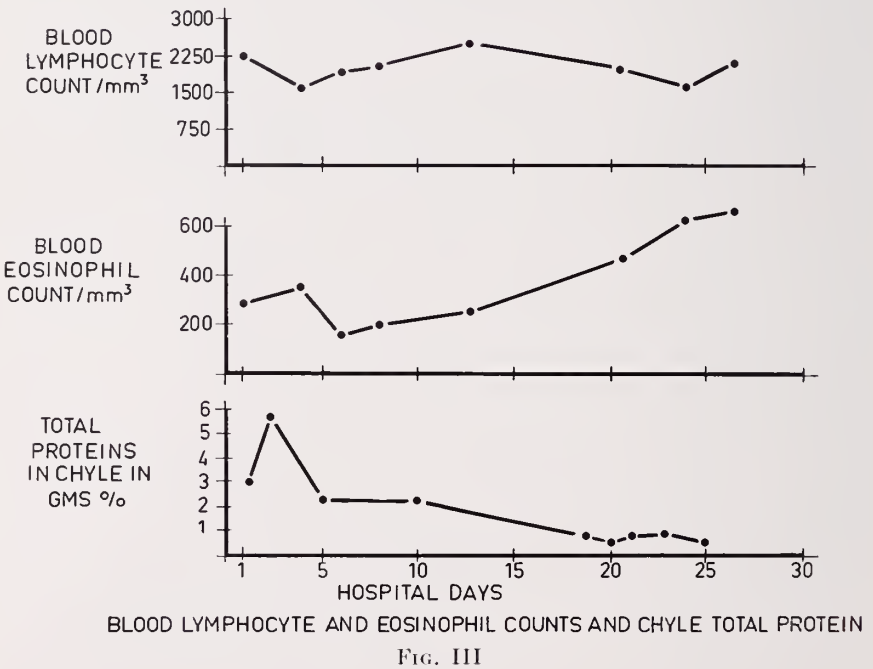
The chylous pleural effusion reaccumulated rapidly and large amounts of chyle were removed at frequent intervals by thoracentesis (Figure II). A total of 4600 cc. was removed in the first nine hospital days. It appeared that the severed or perforated lymphatic trunk had shown little evidence of healing





CHYLE REMOVAL BEFORE AND DURING 66% GLUCOSE INSTALLATIONS

FIG. II



BLOOD LYMPHOCYTE AND EOSINOPHIL COUNTS AND CHYLE TOTAL PROTEIN

FIG. III

spontaneously and it was decided on the advice of Dr. Coleman B. Rabin that an active attempt should be made to seal off the opening, and that 50-100 cc. of a sclerosing solution of 66 per cent glucose be instilled into the right pleural cavity after each thoracentesis. During first eleven days of this regimen the quantity of chyle removed remained quite large, but then a dramatic decrease

in the character as well as the quantity of the fluid was observed (Figure III). It became straw colored and its protein content fell. It is believed that the fluid obtained at this time was no longer pure chyle, but rather was partially exudative in nature and resulted from the pleuritis induced by the hypertonic glucose. All fluid ceased to accumulate on the sixteenth day after the first instillation of 66 per cent glucose. Clinically, the patient felt weak and appeared critically ill during the period when large amounts of chyle were removed from his chest, but he began to improve dramatically as soon as the formation of chylous effusion ceased. He gained weight and strength and was discharged in good condition on the forty-second hospital day. He was found to be asymptomatic and well when examined one year later. The fluctuations in eosinophil and lymphocyte count are graphically demonstrated in Figure III. It can be seen that the lymphocyte count remained relatively constant throughout his course. The eosinophil count, however, which remained normal during the period of chyle loss, showed a definite rise when this ceased. There appeared to be little variation in the lipid composition of the chyle during the period of its rapid reaccumulation (Table I).

This case presented the characteristic clinical features of traumatic chylothorax. Of particular interest was the successful management of the protein loss and the definitive therapy employed.

#### DISCUSSION

*Anatomy:* The earliest lymphatic channels are derived from sprouts of endothelium arising from the primitive venous system. As these sprouts grow they form lymphatic sacs, which then branch to form the lymphatic vessels and the lymphatic capillary plexuses. The jugular lymph sacs sprout from the right and left internal jugular veins, and the upper part of the thoracic duct arises from the left jugular lymph sac. The lower portion of the thoracic duct is derived from the cisterna chyli, which is formed by a series of sprouts from the primitive veins of the Wolffian bodies (1).

The embryonic connection between the venous and lymphatic systems remains a potentially functioning one in adult life at multiple points, as has been repeatedly demonstrated in experimental animals and in humans following thoracic duct ligations.

The thoracic duct is composed of three coats. The inner is a layer of elongated endothelial cells, while the middle coat consists of smooth muscle fibers, elastic

TABLE I  
*Lipid concentration of patient's chyle*

DATE	TOTAL LIPIDS MG%	TOTAL CHOL. MG%	CHOL. ESTERS MG%	PHOSPHOLIPIDS MG%
9/10	2340	150	95	
9/15		150		
9/25		100	60	
9/27	2235	110	60	246

fibers, and a layer of connective tissue (2). The outer coat serves as a protective covering and is made up of connective tissue intermingled with muscle fibers.

The thoracic duct takes its anatomic origin from the cisterna chyli, a saccular dilatation situated anterior to the second lumbar vertebral body. It enters the thorax through the aortic hiatus of the diaphragm and courses upward to the right of the midline between the aorta and azygous vein. At the level of the fifth or sixth thoracic vertebra it veers to the left, ascends through the superior mediastinum behind the arch of the aorta, rises about 4 cm. above the left clavicle and passes laterally to end usually by opening into the junction of the left subclavian vein with the left internal jugular vein (1). The valves are placed closer to one another than those in the veins. There is no regularity to the distribution of valves except for the terminal valve, which prevents the passage of venous blood into the duct and is found constantly within 1 cm. of the end of the duct (3, 4). Van Pernis examined 1081 cadavers and noted that the thoracic duct varied in length from 36 to 45 cm. He found that the location of the cisterna chyli varied in level from D<sub>12</sub> to L<sub>2</sub> (3).

Lowman et al. studied the anatomy of the thoracic duct roentgenographically in cadavers by injecting opaque contrast material into the duct (5). Wide anatomic variations existed in the course of the duct and in the cross anastomotic channels. The duct was observed to bifurcate at various levels and subsequently the divided ducts were found to join. The mode of termination of the thoracic duct was also noted to vary greatly. Single terminations were seen in 75 per cent of the cases, multiple terminations in the rest. The duct emptied most frequently into the left subclavian vein, in other cases into the left innominate, internal jugular, or vertebral veins. This work confirms the earlier dissection studies of Davis (6).

Thoracic ducts in the embryo are bilateral and have numerous cross anastomoses. Persistence of these real or potential channels becomes important in the development of collateral lymph circulation following injury or obstruction to the duct (7, 8). Flandrin in 1691 was the first to conclude that the lymph can reach the blood stream through collateral channels. He ligated the thoracic duct near the subclavian vein in horses and noted only distention of the distal portion on post-mortem examination (9). Lee describes an intrathoracic method for complete ligation of the thoracic duct in the cat. In some cases collateral lymph circulation was established to the right thoracic duct, while in others lymphatico-venous connections were found to exist between the thoracic duct and azygous veins (10). More recently Blalock et al (11) ligated the right and left thoracic duct in dogs and cats, and found that this did not produce chylothorax. This indicated that there must be a number of lymph vessels distal to the obstruction entering the venous system. The same collaterals which were described by Lee were demonstrated. Recovery following ligation of the thoracic duct above and below the diaphragm proves the existence of lymphatico-venous anastomoses within the abdomen (12). Many of these anastomoses have been demonstrated, the majority of them with the inferior vena cava in the neighborhood of the renal veins (13).

TABLE II

*Physical and chemical characteristics of chyle*

- (1) Odorless, or having the odor of recently ingested food
- (2) Specific gravity greater than 1.012
- (3) Total solids greater than 4 per cent
- (4) Finely emulsified, with minute fat globules
- (5) Total fat content between 0.4 per cent and 4 per cent

TABLE III

*Chemical analysis of a specimen of chyle*

Water . . . . .	92%	Phospholipids . . . . .	197 mg%
Solids . . . . .	8%	Total Cholesterol . . . . .	121 mg%
Total Proteins . . . . .	4.73 gm%	Free Cholesterol . . . . .	105 mg%
Albumin . . . . .	3.72 gm%	Cholesterol Esters . . . . .	16 mg%
Globulin . . . . .	1.01 gm%	Total Fatty Acids . . . . .	2.28 gm%
Non Protein Nitrogen . . . . .	20 mg%	Free Fatty Acids . . . . .	0.73 gm%
pH . . . . .	7.42		
Specific Gravity . . . . .	1.015	Sodium . . . . .	122 meq/l
		Potassium . . . . .	2.7 meq/l
		Calcium . . . . .	4.1 meq/l
		Bicarbonate . . . . .	28 meq/l
		Chloride . . . . .	74 meq/l

*Chemistry:* Grossly chyle presents as a milky fluid which on standing separates into three distinct layers: (1) a creamy layer on top; (2) a milky layer in the middle, and (3) a layer of sediment containing cellular elements at the bottom. Table II lists the most important physical and chemical characteristics of chyle (14, 15, 16).

Complete chemical analysis of a specimen of chyle obtained from a case of traumatic chylothorax was carried out by Dittebrandt (17) and is summarized in Table III.

The studies of the cellular content of chyle have revealed the total white count to vary from 2,000 to 20,000/mm. (5). The differential count disclosed 90 per cent lymphocytes (19).

Hoffman et al found the protein content of chyle to range from 1 to 6 gm% (4) while Crandall et al observed a variation from 3.2 to 5.3 gm% (20). Judd and Nix believe that the protein content of lymph in any particular lymphatic vessel is related to the permeability of the lymphatic vessel in question (21). The experiments of Cain et al have given considerable information regarding the factors influencing the protein content of chyle (22). Specimens of hepatic and thoracic duct lymph were obtained in dogs by cannulating the hepatic lymph vessels and the thoracic duct respectively. The hepatic lymph was found to contribute 25 per cent to 50 per cent of the volume of thoracic duct lymph, but the protein content of the hepatic lymph was almost twice as great as that in the thoracic duct. The fat content of chyle parallels the fat content of the diet (18). Sixty to 70 per cent of ingested fat passes along the thoracic duct (4). All



lipid compounds, with the exception of neutral fat, are found in lower concentration in chyle than in plasma (23). Forbes administered Vitamins A and D orally in a case of chylothorax and noted their rapid absorption into the chyle and blood (24). The chyle obtained in cases of non-traumatic chylothorax has been altered in character by filtration through the pleural membranes, while in traumatic chylothorax the composition of the chyle is identical with that in the thoracic duct. In a case of spontaneous chylothorax in a 2 year-old infant only 10 to 30 per cent of the expected fat could be recovered on the examination of the chyle. It was believed that this observation suggested the presence of an obstructive lesion since less than one-third of the calculated concentration of fat was recovered (65).

The existence of a hemolytic agent in thoracic duct lymph has been described (25). This was observed to be present only during absorption of ingested fat and not in the fasting stage. It has been suggested that the quantities of soaps and free fatty acids present in chyle during fat absorption are sufficient to account for the hemolytic action of chyle (25). Another property of chyle which has been attributed to its high fatty acid content is its remarkable resistance to infection (26). Chyle is strongly bactericidal and can remain at room temperature for weeks without putrefaction. *E. Coli* and *Staphylococcus aureus* cultures introduced into pure chyle have failed to multiply (26).

In the past many observers have separated from true chyle two types of fluid which have a similar appearance. These are the so-called pseudochylous and chyliform fluids. The former has been correctly distinguished from chyle and represents fluid which is milky in appearance due to the presence of phospholipids, cholesterol and lecithin. Chyliform effusion, on the other hand, which contains white cells and endothelial cells undergoing fatty degeneration, is now believed to be true chyle.

*Physiology:* The effects of lymphatic obstruction on the survival of the animal, on the differential blood count, and on serum lipid and protein levels have been investigated and have shed considerable light on the pathogenesis of the clinical picture. The fundamental work of Blalock et al has shown the vital importance of some patency of the lymphatic system (13). In a group of dogs and cats, complete lymphatic obstruction was attempted by ligating the lymphatic ducts in the right or left cervical regions, in the chest, and in the abdomen. This was followed by sodium morrhuate injection of the abdominal lymphatics. Those animals which succumbed revealed complete lymphatic blockage at post-mortem examination. In addition, these observers found that in 29 of the 44 experimental animals there was a marked fall in blood lymphocytes, while in 24 of this group of 29 animals there was, in addition, a significant decrease in circulating eosinophils. In 15 of the latter group of 24 animals, an absolute increase in the number of monocytes was noted. Although the fall in lymphocytes could be readily explained by interference with the supply coming from the lymph nodes, no explanation was offered for the fall in eosinophils or the rise in monocytes. A correlation between the return of the cell count to normal and the development of collaterals was demonstrated.

Co Tui et al (27) bled two groups of dogs, one of which had had previous thoracic duct ligations. They found that the return to normal of the plasma protein concentration was considerably slower in this group than in the controls. This supports the belief that the thoracic duct is an important pathway for the return of protein from the capillary filtrates and depot organs back to the blood stream. In a case of accidental ligation of the duct in a human, the total serum lipids were reduced to about 5 per cent of the normal level. The serum lipid level and the differential cell count returned to normal as collaterals developed (13, 28).

In two instances, investigations on lymph have been of aid in the study of fat metabolism. Frazer has postulated that unhydrolyzed triglyceride fat can be absorbed as such from the small intestine, and that it travels chiefly to the thoracic duct via the lacteals, while fatty acids are absorbed mainly into the portal circulation (26). Auld and Needham have lent support to this theory by feeding neutral fat stained with Sudan III to a patient with chylothorax (26). A substantial amount of the dye was recovered in the chyle, whereas no orally administered stained fatty acids were recovered. The dynamic equilibrium between plasma and lymphatic phospholipids was demonstrated by injecting radioactive phospholipids into the blood stream of the dog and recovering these in the thoracic duct lymph after a short interval (29).

Table IV lists the normal and the unusual stimuli to the flow of lymph.

The failure of morphine or of magnesium sulfate to produce definite changes in lymph flow (20) indicates that lymph flow is not greatly affected by changes in intestinal motility, but is determined by the rate of intestinal absorption. Hemorrhage, hypoproteinemia, anemia, and increased vagal tone are the chief factors responsible for decreasing lymph flow (4). Vagotonia acts by producing constriction of the thoracic duct.

TABLE IV  
*Stimuli to the flow of lymph*

- 
- |  |
|--|
| A. Normal stimuli  |
| 1. Ingestion of food (20)  |
| 2. Respiratory movements, particularly the pumping action of the diaphragm (7, 30) |
| 3. Movement of the extremities (31)  |
| 4. Pulsations of arteries adjacent to the thoracic duct (4)                        |
| 5. Rhythmic contractions of smooth muscle fibers in the thoracic duct (2)          |
| 6. Suction produced by the flow of blood in the jugular vein (30)                  |
| 7. Hydration (20)  |
| B. Unusual stimuli   |
| 1. Anoxemia (4)  |
| 2. Anaphylactic shock (4)  |
| 3. Administration of lymphagogues (4)  |
| a. hypertonic or isotonic saline   |
| b. dextrose  |
| c. histamine   |
| d. epinephrine   |
| e. peptones  |
-

The quantity of chyle flow in the thoracic duct has been studied by Crandall (20) in a patient with a thoracic duct fistula. The minimum flow was found to be 23 cc/hr, the average basal flow 56 cc/hr and the maximum flow 234 cc/hr. The pressure in the thoracic duct was measured by Beck (32) by inserting a cannula into the cistern formed by ligating the jugular, subclavian, and innominate veins. The intravenous administration of lymphagogues produced a sharp rise in pressure, while bleeding was followed by a slight fall in both venous and lymphatic pressures.

*Etiology:* The causes of chylothorax fall into two main groups; traumatic and non-traumatic. An estimate of the relative frequency of the two groups can be obtained from Jahsman (16) who, in reviewing 95 cases of chylothorax found that of these 56 (59 per cent) belonged to the traumatic group.

#### *Traumatic Chylothorax*

Three distinct types of trauma may result in the production of a chylothorax: (1) Direct, accidental trauma to the thoracic duct or other major lymphatic vessel. (2) Accidental division of the duct during surgery. (3) Indirect injuries to the back and chest with tearing of the duct.

Hodge's and Bridges' work is of interest in evaluating the consequences of thoracic duct injury (38). These authors found that excision of a segment of the lower thoracic duct resulted in the development of chylothorax in only four out of eight dogs. In the other animals, sealing and fibrosis of the open ends occurred. Therefore, it appears that chylothorax may not necessarily result from a serious injury to the thoracic duct. Numerous examples of direct accidental trauma producing chylothorax have been described. Bullet or shrapnel wounds of the chest (33-37) and wounds in the neck are typical examples. The increasing incidence of injury to the thoracic duct during surgery has paralleled the increasing frequency with which structures in close anatomic proximity to the thoracic duct, such as the esophagus, pericardium, pleura, great vessels, and sympathetic trunks are approached surgically. The importance of the recognition and the immediate treatment of thoracic duct injury at the time of surgery is obvious. Thoracic sympathectomy is the procedure which has produced chylothorax more frequently than any other (7, 38, 4, 39, 28, 40, 12). This complication has also been seen after the following procedures:

1. "Blalock-Taussig" procedure for Tetralogy of Fallot (37, 41)
2. "Potts" procedure for Tetralogy of Fallot (41)
3. Lobectomy (42)
4. Resection of esophagus for carcinoma (7)
5. Resection of a Ewing's tumor of the right 10th rib and vertebra (19)
6. Lysis of pleural adhesions by thoracoscope (7)

Hodge and Bridges believe that injury to collaterals of the thoracic duct probably occurs during many intrathoracic procedures, but that such tears become sealed in a relatively short time (38). The cervical portion of the thoracic duct is most frequently injured in surgical procedures on the left side of the neck for tumor or enlarged lymph nodes. Chylorrhea will develop if such an injury is not recognized and treated (38). Closed or indirect injuries to the chest

producing chylothorax include fracture of vertebrae, fracture of ribs, falling and striking the chest, other thoracic trauma, and hyperextension injuries (67, 5, 41, 42, 43).

In a considerable number of the reported cases which followed indirect trauma the force was apparently not violent and the injury considered to be a minor one. Shakleford and Fisher believe that in these cases sudden changes in the pneumohydrostatic pressure were responsible for the rupture of the thoracic duct (67). This hypothesis is supported by the observations that in several such cases the accident occurred shortly after a heavy meal, when the intraductal pressure is greatest (67, 43). In many of these indirect injuries hyperextension of the spine occurs. During hyperextension the cisterna chyli may be fixed beneath the diaphragm and stretching of the thoracic duct takes place (4). The tendinous edge of the right crus of the diaphragm compresses the stretched, fragile thoracic duct against the vertebral column, produced laceration (44, 45).

Meade points out that the normal thoracic duct is held in place by areolar tissue which permits it to move freely (46). He believes that it cannot be ruptured in indirect injuries unless it becomes fixed to the vertebrae. In all of his cases of indirect injury there was evidence of fixation, produced either by congenital anomalies or old fractures of dorsal vertebrae, inflammatory tissue in the chest or prior severe back injury. In four of the five cases reported there was a precipitating traumatic episode which could be interpreted as representing an overstretching of the fixed duct. The authors believe, however, that a third factor, namely, an increased fragility of the duct, also exists in these cases.

Severe cough has been considered of etiologic significance in cases of chylothorax (12, 68, 47). Birth trauma was responsible for a case in a 15 day-old infant (48).

#### *Non-Traumatic Chylothorax*

Blalock et al ligated the superior vena cava just distal to the entrance of the azygous vein in 13 dogs (11). Seven of these developed chylothorax in 9 to 25 days. The venous pressure rose in all cases, but the height did not correlate well with the development of chylothorax. Chylothorax did not develop in any of the four animals in which the thoracic duct was ligated at T-7. When the superior vena cava of these animals was ligated 7 to 13 days later, chylothorax did not occur either, indicating that collaterals had already become functional at this time. In a later communication (23), the authors report that in 47 animals in which the superior vena cava was ligated chylothorax appeared in 28. This work indicates that mere blockage of the duct, as by tumor, for example, would not produce chylothorax. Numerous cases have been noted in which infectious or malignant obstruction to the thoracic duct have occurred without any chylous accumulations (49). Meade et al believe that a tumor must invade the duct, and that fixation of the duct with subsequent tearing during hyperextension would then produce chylothorax (50). Obstruction of the superior vena cava is another cause of chylothorax, which has been noted clinically as well as experimentally.

The neoplasms most frequently associated with chylothorax are Hodgkin's



disease, retroperitoneal sarcoma, and carcinoma of the stomach (31, 51, 52). Lymphangiomas are subject to periodic infection, producing swelling of these tumors and sometimes rupture. In a case described by Swift and Neuhoof (45) the lymphangioma which became infected and ruptured arose from the thoracic duct and produced chylothorax. The authors suggest this as a possible explanation for cases of chylothorax in children, in whom no obvious etiology was present, and in whom the appearance of chylothorax was preceded by a respiratory infection. Lymphangiectasis extending up through the abdominal lymphatics to the chest has also been reported to produce chylothorax (49).

In analyzing the etiology of 13 cases of chylothorax in infants under one year of age, 10 cases were found to be spontaneous, one case traumatic, one case due to tuberculous nodes and one case with cause unknown (53). No case of spontaneous chylothorax has been noted in children above the age of one year, implying that spontaneous cases are due to congenital defects (14). In the cases of spontaneous chylothorax hypoplasia or defects of the thoracic duct are noted at post-mortem examination (24). Absence of the thoracic duct at post-mortem has been reported in a case of chylothorax in an infant.

Other etiologies of non-traumatic chylothorax reported are thrombosis of the left subclavian vein, perforating lymphangitis, aneurysm of the thoracic duct, filariasis, cirrhosis, tuberculosis of mediastinal nodes, and tuberculous paravertebral abscess (49, 52, 54, 44, 49, 31). Chylothorax associated in one case with miliary tuberculosis only, and in another with cavitary tuberculosis have been reported (66). A case of chylothorax resulting from thrombosis of the thoracic duct secondary to atherosclerosis has been reported (49). Griffith describes the case of a 60 year-old man with chylous ascites and chylothorax who showed progressive deterioration and death (15). At autopsy the thoracic duct could not be found, nor was there any evidence of an obstructive or invasive lesion in the region where the duct is usually found. The possibility is suggested that the thoracic duct is subjected to degeneration and atrophy in old age.

*Clinical Picture:* Because of the rarity of chylothorax the diagnosis is seldom even suggested until the thoracentesis is performed. This condition often presents certain characteristic clinical features which should make one suspect the diagnosis earlier. In cases of traumatic etiology, as in the case presented, there usually is a latent period of several days to weeks following the trauma before the development of symptoms and signs. This delay corresponds to the time it takes for the extravasated chyle in the mediastinum to break through the parietal pleura into the pleural cavity. Rarely the chyle may be detected in the mediastinum before chylothorax actually develops. It is valuable, therefore, to have lateral and oblique view of the chest in order to recognize fluid in the posterior mediastinal pleural segments in any suspected case of thoracic duct injury.

Brown demonstrated a rounded shadow on the right heart border by x-ray which was interpreted as an enlarged hilar node (55). Shortly thereafter the cystic mass ruptured into the pleural cavity and chylothorax developed. It is this sudden rupture of chyle into the pleural cavity that probably explains why



the onset of symptoms and signs is so frequently abrupt. Lowman et al reported a case in which chest x-rays were at first negative but 20 minutes later showed marked accumulation of fluid due to rupture of a retropleural chyloma (5). The history is frequently of a patient who is asymptomatic days or weeks after a severe or trivial accident and who suddenly complains of dyspnea and severe unilateral pleuritic pain, most often right-sided. A shock-like picture may rapidly ensue in which the pulse becomes imperceptible and the patient collapses. In Peet and Campbell's case of chylothorax the patient was recovering from splanchnicectomy on the 9th postoperative day when he suddenly became cyanotic and went into shock with an unobtainable blood pressure (40). This shock-like picture is probably analogous to that seen in a small spontaneous pneumothorax and may depend on sudden changes of pressure relationship within the chest (69).

The symptoms and signs are usually rapidly relieved by thoracentesis with the removal of the fluid. The milky appearance establishes the true nature of the fluid with two notable exceptions: 1) A concomitant hemothorax can mask the identity of the effusion. After the blood clears the chylous nature becomes apparent (42). 2) Pus can occasionally be mistaken for chylous fluid, therefore, microscopic examination is important (39). The lipid nature of the fluid should also be confirmed by stain, such as Sudan III. It should be noted that chyle is usually orange-yellow in color in the newborn (56). Of diagnostic import also is the rapid fall of circulating lymphocytes and frequently of eosinophils. This is usually sustained until the chyle ceases to reaccumulate.

The reaccumulation of chyle is usually rapid, frequently necessitating daily thoracentesis. A total aspiration of 80 liters of chyle from the chest has been reported (12). Little et al removed over 500 liters of chyle from the pleural and peritoneal cavities in an 18 month period from a patient with chylothorax and chylous ascites (57). The constant loss of large quantities of this protein and fat rich fluid results in dehydration and weight loss. The patient becomes weak, thirsty and oliguric. The serum proteins as well as blood fat levels rapidly fall to low levels, and eventually if the process is not halted, the patient dies from inanition.

In a minority of cases a more complicated clinical picture occurs. Chylothorax from underlying malignancy frequently is associated with chylous ascites (49). Chylopericardium is rare and only four cases have been reported (49). Buxton and Morrison reported a patient with a torn esophagus and thoracic duct who vomited chyle and, therefore, did not develop chylothorax (58). The only published case of chylopneumothorax was recently reported in a patient who developed chest pain and dyspnea, after a sudden exertion (59).

*Medical Treatment:* The treatment of chylothorax has undergone a significant change in recent years with the advent of definitive surgery. In the case reported a definitive form of non-surgical treatment was used which offers promise of an effective and simple method of treatment. (To be reported in detail in a subsequent paper by Rabin and Schwartz.)

The objects of medical management include:

1. Maintenance of nutritional status.
2. Relief of respiratory symptoms.
3. Promotion of healing of the fistula.
4. Treatment of associated or underlying disease.
5. Prevention of complicating infection.
6. Careful observation to determine whether surgical intervention is indicated.

The constant loss of large amounts of fluid rich in protein and fat causes rapid inanition and dehydration unless quickly and vigorously combatted. A diet should be given which is high in calories, protein, carbohydrate and vitamin content and which is low in fat content. It is desirable to restrict the fat intake for two reasons: 1) to decrease the amount of chyle formed; 2) to allow ample intake of protein and carbohydrate which can be utilized by the body in contrast to the fat, the majority of which will be promptly excreted into the pleural cavity and lost to the outside. Supplementary intravenous feedings are just as essential. Chyle has been given in the past, both intravenously and intrasternally on numerous occasions (19, 24, 34, 39, 40, 43, 57, 60, 61, 66). The occurrence of sudden unexplained death following its use makes it unsafe, especially since other substances are available which are safe and more efficacious. Amino acid solutions, plasma, and blood have been used widely. Whole blood should certainly be used if anemia develops. However, as a means of maintaining normal plasma levels of protein we have found human serum albumin to be an effective product. It is administered easily and quickly without untoward reaction and does not carry the same risk of future homologous serum jaundice as does plasma or blood. If given in sufficient quantities it will probably maintain the plasma protein levels at normal values for an indefinite period of time.

Thoracentesis, frequently daily, must be done to relieve respiratory embarrassment due to the rapid reaccumulation of chyle in the chest. Although Jahsman feels that this should be its sole purpose, and that the increased fluid pressure may serve as a tamponade and help close the fistula (16), most observers take the opposite point of view. Effler states that chyle is an irritant and causes a pleuritis (8). He suggests continuous suction which allows expansion of the lung with approximation of the visceral and parietal pleurae. The two pleural surfaces will then form a firm symphysis and close the chyle fistula. The fibrinous exudate resulting from chylothorax can also serve an adverse purpose if the lung is allowed to remain collapsed. Pleural thickening may occur which necessitates decortication (35, 50, 59, 69). It seems advisable, therefore, to keep the lung expanded by frequent thoracentesis, or if this is not possible, by constant underwater drainage.

A more direct nonsurgical approach to closing the chylous fistula has been attempted by introducing an irritating substance into the pleural cavity. Schnug and Ranshoff introduced sterile broth into the pleural cavity in an effort to cause an obliterative pleuritis (34). The reaccumulation of chyle promptly ceased but the authors felt that no conclusions should be drawn because a phrenic crush had been performed two weeks previously. Matson and Stacy used a 1 per cent solution of gominol in oil over a 2 month period with cure of

the chylothorax (36). Gordon reported a favorable result with a 1:3000 saline solution of azochloramid (62). In evaluating any method of treatment, however, it must be kept in mind that approximately 50 per cent of the cases of traumatic chylothorax will be "spontaneously" cured by supportive treatment and repeated thoracentesis.

Treatment of an underlying disease must not be neglected. In chylothorax secondary to malignancy radiation may be indicated (5, 31). Radiation was administered after the diagnosis of Hodgkin's disease had been established in a patient with chylothorax, and after the duct had been ligated (51). The patient improved. Antibiotics should be used routinely to prevent the complication of an unrelated infection in a patient who is already severely ill and probably has a lowered resistance to infection. However, no case has been reported of empyema developing in the pleural cavity secondary to thoracentesis or surgical intervention, undoubtedly because chyle is bacteriocidal in nature.

*Surgical Treatment:* The modern surgical approach to chylothorax is primarily concerned with repair or ligation of the duct in its intrathoracic or supraclavicular portions. Other surgical procedures, such as phrenic section, have been used in the past with varying results. According to Nowak and Barton the objects of phrenicotomy are: 1) Elongation and narrowing of the crurae of the diaphragm with apposition of the diaphragmatic and mediastinal parietal pleurae. 2) Decreased aspirating action on the open thoracic duct (44). Phrenic section has given inconsistent results (30, 34).

A more definitive and relatively benign procedure is the ligation or repair of the duct in its supraclavicular portion. This procedure is indicated if the duct has been torn in the supraclavicular area or if there is pressure on the duct from a fractured clavicle (16). The duct is found most easily behind the carotid sheath where it can then be ligated or traced to the area of injury and repaired (42). Loe suggests burying the end of the duct in a muscle or behind the sheath of a vessel if possible to give added support because of the increased pressure within the duct after ligation (42).

Thoracotomy is necessary for surgical treatment of injuries to the duct in its intrathoracic course, and is indicated if medical treatment has failed to halt the accumulation of fluid. There can, of course, be no set rule as to the length of time that conservative measures should be attempted. If the patient's general nutritional status can be well maintained by the measures previously outlined, then the patient should have a medical trial of at least several weeks. On the other hand, if the patient's general condition is deteriorating despite supportive measures, intrathoracic exploration should be done at once. It is a procedure which in recent years has been demonstrated to be effective and usually safe (37, 41, 47, 51, 63). The patient may be fed a colored dye in cream or oil several hours before the operation to distend and color the thoracic duct for easier identification. Klepser believes coal tar dyes, particularly Sudan III, are preferable to vegetable and oleomargarine dyes for staining chyle (64). The surgical approach may be through the left or right side. Lampson's approach to the thoracic duct is through the left chest (47). The mediastinal pleura is slit, the

esophagus is retracted anteriorly, and the aorta to the left and posteriorly. The thoracic duct distended and colored by the dye is visualized. Meade utilizes the right-sided approach (46). This approach may be employed in cases of bilateral chylothorax where the duct should be ligated just above the diaphragm (63).

The decision as to whether the duct should be ligated below the defect or whether the defect should be searched for and repaired has not been fully settled. It seems to us that if the duct can be visualized and ligated at a point definitely below the defect, this should be done, since it has been the experience that cases so treated show cure of the chylothorax and absence of untoward effects. Lampson and Meade ligated the duct above the diaphragm and their patients were cured (46, 47). On the other hand, Morris and Polk identified the defect in the thoracic duct at D-11 and ligated it with silk, and the patient was cured (35). Shumacker and Moore reexplored two patients with chylothorax following surgical injury to the thoracic duct (41). In both cases the opening in the mediastinal pleura through which the chyle was leaking was observed. In neither case could the duct be identified. Therefore, gelfoam was packed into the defect and suture ligatures were placed around the opening in the pleura and tightened. The reaccumulation of chyle ceased in both cases. When the duct is ligated high pressures develop distally immediately afterwards, but rupture has not been noted to occur. The procedure advised by Hodge and Bridges (38) of ligating the azygos vein close to the diaphragm, dividing the intercostal vein above the lesion, and implanting the duct into the vein is probably unnecessary in view of the excellent results of simple ligation. On the other hand, a small portion of the duct should probably be resected after ligation in order to prevent recanalization, and to obtain histological verification of the structure and determination of any pathological process (46).

Injuries occurring during operation should be immediately repaired or the duct ligated. Ehrenhaft and Myers suggest closing the opening with suture ligatures, if possible, and if not feasible, with a muscle stump or gelfoam (28).

*Prognosis:* The prognosis of chylothorax has been considerably altered in the last decade by the new medical and surgical advances previously described. The figure of a 50 per cent mortality so frequently quoted in the literature (16, 39, 50), is no longer acceptable. The prognosis will continue to remain poor in two situations:

1. Chylothorax associated with underlying disease. The underlying disease is frequently metastatic tumor or lymphoma; hence, the outlook is grave.

2. Chylothorax in the newborn is a dangerous situation but even here recoveries have been reported (18, 56).

The remainder of the cases of chylothorax, traumatic and idiopathic in nature, can now be handled much more adequately. The judicious use of the techniques mentioned before should make it possible to cure the majority of cases.

#### SUMMARY

A case of traumatic chylothorax is presented. The patient recovered after receiving therapy consisting of repeated thoracentesis, replacement of protein



loss, and the repeated instillation of 66 per cent glucose into the pleural cavity.

The origin of lymphatic channels from the venous endothelium, and the significant histological and anatomical features of the thoracic duct are discussed. The wide anatomic variations in the thoracic duct and in the cross-anastomotic channels is stressed.

The physical and chemical properties of chyle are presented. The experimental evidence indicating the necessity for some patency of the lymphatic system for life is cited. The most important stimuli to the flow of lymph are listed.

Trauma, the most frequent cause of chylothorax may be due to direct injury to the thoracic duct, accidental division of this structure during surgery, or indirect injury to the back with tearing of the duct. Non-traumatic chylothorax in adults is usually produced by neoplastic invasion of the duct, while in infants it is most frequently due to congenital defects of the thoracic duct.

The common clinical features are described as are some of the variants. A high calorie, low fat diet, intravenous serum albumin, thoracentesis, and the introduction of irritating substances into the pleural cavity are the most important conservative measures available in the treatment of chylothorax. Thoracotomy with ligation or repair of the duct should be reserved for the patient whose condition deteriorates despite adequate conservative therapy.

The prognosis is now quite favorable in adults with traumatic chylothorax, but remains poor in the cases associated with malignancy, and in the newborn.

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## LIPOMA OF THE COLON<sup>1</sup>

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Lipoma is the most frequent intramural tumor of the colon. Preoperative diagnosis is rarely made. The purpose of this paper is to present the roentgen features in five proved cases. These appear to be sufficiently characteristic and distinctive to permit the suggestion of the correct diagnosis in the majority of instances.

We are concerned in this paper primarily with lipomata which present as polypoid lesions. Therefore, we have not included cases with intussusception as the predominant clinical and roentgen feature. In the presence of intussusception, the diagnosis of the type of tumor is extremely difficult because of the inability to separate it from the rest of the intussusceptum. The rare subserosal colonic lipoma is not included in the present discussion since it does not present as an intraluminal filling defect.

Lipomata of the colon are said to occur with equal frequency in males and females. They are most frequently seen in the third to the sixth decades. In a series reported by Long et al (1), 0.5% of 13,000 autopsies showed lipomata of the colon. They represent therefore the second most common benign tumors of the colon, exceeded in frequency only by adenomatous polyps (1, 2, 3, 4). Lipomata are found most often on the right side of the colon. In a review of the literature, Pemberton and McCormack (4) describe the following distribution: 50 in the cecum and ascending colon, 15 in the transverse colon, 14 in the sigmoid, 12 in the rectum, 11 in the descending colon. In Runyeon's collected series (5), 62% of the lipomata were proximal to the splenic flexure.

It is generally agreed that colonic lipomata are true benign tumors composed of adult fat cells enclosed in a thin or thick fibrous capsule. In the majority of instances, the lesion is single and presents as a lobulated soft submucosal tumor. When small, it is usually sessile. As it increases in size, it becomes pedunculated in characteristic fashion. The mucosa over the lipoma often ulcerates and this may result in bleeding.

*Roentgen Diagnosis:* The roentgen features to be described apply specifically to lipomata of considerable size, 3 or more centimeters in diameter. Differentiation of small lipomata from adenomatous polyps is difficult and will be discussed under differential diagnosis. Fortunately, most of the lipomata that cause symptoms are of considerable size. Long et al (1) made the diagnosis of lipoma on one occasion and suggested it in two other cases, apparently primarily on the basis that the intraluminal filling defect on double contrast enema examination did not show a "water" density. They, however, believe that ordinarily it is not possible to distinguish these lesions from other polypoid lesions. Weisberg (6) states that roentgen examination cannot be depended upon to differentiate

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FIG. 1a



FIG. 1b



FIG. 1c

FIG. 1a. D. S. Large lipoma in ascending colon showing sharp, somewhat angular contours and pear shape.  
 FIG. 1b. D. S. Same examination — globular shape, sharp smooth contour.  
 FIG. 1c. D. S. After evacuation, lipoma appears as a sausage-shaped intraluminal mass with wide pedicle.



FIG. 2a



FIG. 2b

FIG. 2a. B. S. Lipoma of hepatic flexure: pear-shaped, intraluminal defect with sharp, smooth contour.

FIG. 2b. B. S. After evacuation, broad pedicle with wide area of insertion into bowel wall is evident. Pedicle appears longer than seen on the filled bowel.



FIG. 3. E. K. Lipoma of hepatic flexure: large smooth, sharply demarcated lobulated intraluminal defect with broad attachment to bowel wall.





FIG. 4a



FIG. 4b

FIG. 4a. I. B. Lipoma of descending colon: large, smooth, spherical intraluminal defect with broad attachment to bowel wall.

FIG. 4b. I. B. After evacuation, marked elongation of the lipoma. Bowel wall contracted down around tumor.

lipoma from carcinoma. Dallas (7) anticipated that evacuation and double contrast films of the colon might make it possible to make the pre-operative diagnosis of lipoma more frequently.

The roentgen features of diagnostic significance demonstrated in the reported group of cases were not difficult to delineate. With the colon filled with barium, the lesion presented itself as an intraluminal defect with sharp smooth contour (Figs. 1a, 1b, 2a, 3, 4a). One or more large lobulations were occasionally identified (Fig. 3). When the margins of the defect were not spherical, they appeared to be composed of segments with somewhat angular junctions (Figs. 1a, 5). A striking feature was the fact that the shape of the filling defect was not constant (Figs. 1a, 1b). This was evident, not only on repeated roentgenograms during filling of the bowel, but particularly when the configuration of the defect in the filled colon was compared with that after evacuation (Figs. 1a, 1b, 1c, 4a, 4b). The films after evacuation showed the effect of contraction of the bowel wall around the tumor. As a result of the unusual softness of the lipoma, the contrac-



FIG. 5. A. F. Double contrast examination. Lipoma of transverse colon. Smallest lipoma of the group. Peculiar angular contours, no pedicle demonstrated.

tion of the bowel wall produced a characteristic, elongated or sausage shape to the intraluminal defect. All of these larger lipomata could be demonstrated to have a pedicle of variable length. Characteristic features of the pedicle, in contrast to the pedicle of an adenomatous polyp, were its considerable width and also the considerable width of the base or attachment of the pedicle to the bowel wall (Figs. 2a, 2b, 3, 4a).

Since fatty tissue absorbs less radiation than "soft", i.e. water density, tissue, it is theoretically possible to recognize a lipoma of the colon by its unusual radiolucency. In actual practice, this is not a reliable sign. Even a small amount of barium around a soft tissue intraluminal defect, specifically a polyp, frequently produces a false impression of a striking radiolucency (Fig. 6).

*Differential Diagnosis:* There is usually little difficulty in differentiating lipomata of the colon from carcinomata. The only type of carcinoma that may come into consideration is the so-called villous adenoma. The smooth contour of lipomata and the fact that a broad pedicle is present helps to differentiate them from other tumors. The base of a villous adenoma is broad and the surface of the tumor is irregular. The usual problem in differential diagnosis is to distinguish lipomata from adenomatous polyps which also show a pedicle.



FIG. 6. H. F. Double contrast examination. Sigmoid polyp. The striking lucency of the defect is a result of the small amount of barium surrounding it and is not caused by an intrinsic radiolucency of the polyp.

Adenomatous polyps are usually small, 1 or 2 centimeters in their longest diameter and ellipsoidal in shape. Despite their small size, a pedicle of significant length is frequently demonstrable. In contrast, lipomata of this size are usually sessile (Fig. 5). Adenomatous polyps do not change their shape and may show a fine "mulberry" surface. The contours of these small sessile lipomata are sharply demarcated (Fig. 5), and may show changes in configuration depending on the degree of contraction of the bowel wall. Adenomata are frequently multiple and more common on the left side of the colon. Benign polyps do not attain the large size of most of the symptomatic lipomata.

We have no experience with other types of intramural colonic tumors, such as myomata or fibromata. Tumors of these types, presenting as intraluminal filling defects, are exceedingly uncommon. Apparently such tumors may develop a pedicle in similar fashion to lipomata. However, changes in shape of the tumor defect are unlikely since, in contrast to lipomata, they are described as being hard in consistency (8).

The pre-operative diagnosis of lipoma of the colon is of more than academic interest. Certainly, the differentiation from carcinoma of the colon is of importance in giving a prognosis and in preventing the possibility of an extensive resection. Moreover, if the suggestion of lipoma is made to the surgeon before operation, he will then be inclined to identify the nature of the tumor before even local resection is performed. Lipomata of the colon can be treated by colotomy and local excision. There is no instance of recurrence in the literature. Malignant transformation (or a primary liposarcoma of the colon) apparently is also excessively rare, if it occurs at all.

#### SUMMARY

1. According to the literature, the correct preoperative diagnosis of lipoma of the colon is rarely made.
2. The roentgen features in five proved cases of lipoma of the colon are reported.
3. It is considered that the roentgen features described are sufficiently distinctive to permit the correct diagnosis in many cases.

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## RECENT TRENDS IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES\*

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The last decade has witnessed the introduction of new drugs and procedures in the treatment of peripheral vascular diseases. The most valuable addition has been the group of antibiotics. These have profoundly altered the clinical behavior of cases with infection and gangrene. The resulting changes in therapeutic concept and practise can be considered under several headings.

### AMPUTATION

This procedure is essentially one in which a line of demarcation is selected by the surgeon at a level which he considers a likely one for prompt healing. Formerly a thigh operation was common, even in the absence of diabetes, for arteriosclerotic gangrene of a toe or portion of the foot. The frequency of local or systemic complication made amputation at a lower level unwise for the majority of patients. With the advent of the antibiotics, with improvement in metabolic regimens and with a more discerning evaluation of the individual patient, it has become commonly possible to perform exeresis at lower levels.

Amputations below the knee are now being done that were formerly considered inadvisable or impossible (1). The introduction of the transmetatarsal procedure has been a real contribution (2). When successful it means that the patient retains an extremity which is practically as useful as before and with an almost normal gait.

It is true that immediate hospital stay tends to be prolonged where there is a conscientious attempt to keep levels of amputation as low as possible. It is not true that this represents an economic loss, since the saving of weeks in some cases by early high amputation may result in others in avoidable years of invalidism with dependence on friends and family for economic sustenance and bodily comfort.

### ARTERIAL EMBOLISM

The majority of these cases occur in patients with rheumatic heart disease. The difficulties in the management of these patients have been reduced by the promising results of valvular surgery. Embolic occlusion of a major artery is no longer an unfortunate incident in the downhill course of a hopeless cardiac but rather a remediable condition in a patient whose chief lesion may well be amenable to subsequent commissurotomy. In this connection it may be noted that in a series of over five hundred mitral commissurotomies with a pre-operative arterial embolism incidence of twenty per cent, Glover found not a

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single embolic episode despite a mean post-operative follow-up of three years (3).

In the inferior extremity, the treatment of choice for arterial embolism is removal of the embolus except in those patients where there is early unequivocal evidence of complete tissue viability with presumptive return of full function. The unfortunate custom of routinely administering drugs and injecting procaine in the neighborhood of the lumbar sympathetic ganglia with consequent delay in operation frequently leads to gangrene or serious impairment of extremity function. This does not mean that careful examination, evaluation and judicious employment of these ancillary measures are to be abandoned in favor of rushing all patients to the operating room for embolectomy. It merely means that vacillation, pointless delay and vagueness in therapeutic attack frequently accompany a regimen of drugs and procaine blocks. It is true that not all embolectomies are successful but the great majority are limb saving if promptly and properly performed within twelve hours of onset (4).

Embolectomy, by contrast, is commonly not necessary in the superior extremity. The richness of the collaterals and the infrequency of degenerative disease apparently protect the tissues so that warmth, sedation and stellate ganglion block usually suffice. It is not uncommon to witness return of the radial pulse within a fortnight of the lodgment of an embolus where the profunda branch leaves the brachial artery.

#### PERIPHERAL ARTERIAL THROMBOSIS

With the exception of those instances due to external trauma which can presumably occur at any point in the arterial tree, this category consists largely of the characteristic lesion at the lower end of the femoral artery as it winds about the adductor tubercle from Hunter's canal into the popliteal space. The differentiation of this condition from embolic occlusion should be and can be promptly made.

Whereas embolism occurs in the presence of cardiac irregularity at any age in patients free of metabolic disease, thrombosis takes place in the absence of arrhythmia in the middle aged or elderly patient suffering from degenerative arterial disease and, not infrequently, diabetes. The exact localisation of the site of occlusion by palpation of the pulses and careful oscillometry will clinch the diagnosis since emboli lodge at the femoral or popliteal bifurcations whereas thrombosis occurs in the course of the vessel.

The treatment of this arterial lesion is properly conservative. It includes sympathetic blocks, intermittent or continuous, and the immediate institution of an anticoagulation regimen which should be maintained at least a fortnight. Sedation, general body warmth, elevation of the head of the bed and physical protection of the affected extremity are worthwhile additional measures. The clinical behavior of each case determines the pattern of treatment.

Recovery ranges in degree from complete restoration of all the pulses with full function within six weeks to the opposite picture of the cold, painful, pulseless

extremity subject to intermittent claudication on movement. In the absence of severe heart disease, lumbar sympathectomy may be of help. If this does not benefit, then resection of the affected length of vessel with replacement by graft should be considered.

#### PERIPHERAL ARTERIOSCLEROSIS OBLITERANS

This generic term includes almost all varieties of arterial insufficiency due to organic involvement with the exception of Buerger's disease. The pattern of anatomic change, the rapidity of extension of the disease process and the distribution of small, local thromboses fashion the clinical picture. If the history is elicited in detail and the examination carefully done, it will be possible to segregate those cases in which segmental arterial disease is a likelihood. Leriche's syndrome can be readily suspected as can thrombosis of the iliac portion of the arterial trunk. Arteriography and aortography are essential in this determination.

The introduction of endarterectomy and, particularly, vessel graft substitution for diseased segments of major arteries place a new and heavy responsibility on the physician confronted with this type of case (5, 6, 7). He can no longer satisfy himself with a cursory examination and the administration of the latest panacea from the drug-houses. He must realize that a certain proportion, perhaps ten per cent, are patients with segmental arterial disease which can be defined by arterial contrast studies.

In addition to autogenous vein grafts and homologous preserved arterial ones, a new vessel substitute has been provided by plastic cloth tailored to fit the defect (8).

#### LUMBAR SYMPATHECTOMY

There are few topics characterised by a wider divergence of opinion or a poorer quality of clinical exposition. It is at times difficult to realize that the disputants are discussing the same procedure and its effect on the same general type of patient. The problem is one of selection of cases. Although there are responsible investigators (9) who feel that every extremity exhibiting signs of arterial insufficiency should be given the benefit of sympathectomy because of a possible long term effect on the development of collaterals, some patients, particularly those suffering claudication due to diffuse arteriosclerosis, show no improvement after this procedure. Certainly, where there is any evidence of a spastic element in any given case, sympathectomy is far more effective than the oral, intramuscular or intra-arterial administration of any sympatholytic substance.

Recently, a more complete denervation has been suggested (10). If it can be assumed that sudomotor and vasomotor fibres have the same pattern of distribution, then the higher operation including Th 12, is a more physiologic procedure (11).

## THROMBOPHLEBITIS, PULMONARY EMBOLISM, THE POST-PHLEBITIC SYNDROME

The compact grouping of these formidable conditions in a section heading is rather amusing when one considers the library stacks filled with the huge literature on the subject.

It is important to develop a *modus operandi* in the treatment of the various stages of this affliction because there is no more variable, insidious disease process than this disorder of the venous system.

In the acute phase, the anticoagulants form the basis of therapy except where there is specific contra-indication to their use. The length of treatment varies with the individual case and the prognosis should always be guarded. When embolism occurs, the regimen remains one of effective anticoagulation unless there is evidence of recurrent embolisation. If this occurs, then isolation of the likely feeding focus from the venous trunks is indicated. In the majority of cases this is satisfied by ligation of the femoral veins just distal to the profunda branches. In a minority of cases, this does not interrupt the embolic process, the assumption being that a pelvic source is to blame. Rarely emboli can originate above the ligature tied about an apparently normal femoral vein.

Inferior vena cava ligation has been advocated in this problem (12). There is reason to believe that the morbidity following this operation is higher than the literature would indicate. The important point is that each case must be individualised. This disease lends itself to judgment not statistics.

One of the unsolved enigmas is that of the post-phlebitic syndrome. The morbid anatomy of this condition was once thought to be chronic inflammation of the venous trunks with cicatricial incompetence of the valves. Operative treatment has been devised on this basis (13). The results are not conclusive and there has recently been further questioning of the accuracy of phlebography in evaluating this condition (14). For the present, a regimen of rest and prosthetic support is advisable in the majority of cases with the operative procedures to be reserved for those not responding to a fair, prolonged trial of conservatism.

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## THE CLINICAL STATUS OF VAGINAL CYTOLOGY<sup>1</sup>

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Despite concentrated efforts to reduce deaths due to malignancy, the cause and cure of cancer remains unsolved. Techniques in surgery have improved, x-ray and radium therapy have been modified with increasing success, and innumerable painstaking investigations have contributed greatly to a better understanding of this disease. Yet, until such time when cancer will be found amenable at any stage to treatment, emphasis must be placed on early recognition. Experience has indicated that control is most effective when the malignancy is small, early, and localized. The widespread publicity given to cancer control has undoubtedly resulted in an increasing number of patients presenting themselves for medical care in the initial stages of the disease. It is felt that if the facilities at present available for early diagnosis were fully utilized by an informed medical profession, results would be greatly improved.

The Papanicolaou vaginal smear has achieved universal recognition in the past few years as a method of diagnosing carcinoma. This technique is extensively utilized by some Institutions and Clinics, and haphazardly by others. Different impressions have been gained by both the laity and physicians of its significance and value. A summation of the present clinical status of vaginal cytology seems in order. "What statistical evidence has been accumulated in regard to the value of the Papanicolaou smear in the diagnosis of carcinoma of the female genitalis? Of what value are the smears in the detection of equivocal or potential carcinoma of the cervix?"

Exfoliative cytologic studies have been shown to be a useful means of diagnosing cancer of the uterus. Particularly encouraging are the results obtained in the diagnosis of squamous cell cervical carcinoma. Papanicolaou and Trout reported a 96.8% accuracy in the diagnosis of this type of malignant cervical lesion (1). Isbell and Hertig's results were 97.5% correct (2). Our findings have been right in 94% of our cases. Others have indicated similarly good results (3, 4, 5).

Intraepithelial carcinoma, or carcinoma in situ of the cervix has received much attention in recent years (5, 6, 7). As a consequence, there has been decided stimulation in the search for cervical cancer in the noninvasive stage. The cells exfoliated from an intraepithelial carcinoma of the cervix do not differ from those cast off by an early invasive lesion. The character of invasiveness, therefore, cannot be determined by cytologic smear studies. However, the presence of a positive smear, necessitates further investigation and differentiation by adequate cervical biopsy. Reports indicate that an intraepithelial carcinoma of the cervix will manifest a positive smear in 70% to 90% of cases. Younge (8) found a 71% degree of accuracy, Foote (9) 77.8%, and Gusberg 80%. In Gra-

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ham's (10) series of 40 cases of carcinoma in situ, the smear was positive in 87 %. In five cases of proven carcinoma in situ we observed, all showed positive smears.

It is obvious, however, that in patients in whom the malignant lesion is clinically asymptomatic, the false negative smear will give unfortunate information. During the non-invasive stage, no symptoms will be present, and all physical signs will be minimal. It is particularly in this type of case that the vaginal smear can make its maximum contribution. Papanicolaou has emphasized that in adenocarcinoma of the cervix, malignant cells are shed early and are readily detected by vaginal spread (1). Cuyler has reported a 95.3 % degree of accuracy in endocervical carcinoma (11). Our diagnosis has been correct in 91 % of cases. In general we may say that the accuracy in diagnosing adenocarcinoma of the cervix closely parallels the results obtained in squamous cell cervical carcinoma. The smear in itself is of no value in differentiating between fundal carcinoma or adenocarcinoma of the cervical canal.

The use of exfoliative smears for determining the presence or absence of corpus carcinoma is less impressive. Although, Papanicolaou (1) reported a 90.7 % degree of accuracy in adenocarcinoma of the fundus, all others have reported less encouraging results, the figures ranging from 66.7 % to 83.4 % accuracy (2, 3, 5, 12). Prior to the use of endometrial cannula aspirations our series included false negative reports in 26 % of the malignant cases. Since this additional step was instituted, however, our false negatives have decreased to 8 %.

From a perusal of the literature it is apparent that the vaginal smears were, and to some degree still are more accurate in the diagnosis of cervical cancer than fundal carcinoma. There are several reasons:

1. Endometrial aspirations were not taken routinely until recently.
2. The malignant cells cast off from the uterine fundus degenerate during the time required for them to traverse the uterine and cervical canals to the vagina.
3. Continued bleeding may wash away the exfoliated cells, or dilute them.
4. Cervical stenosis, pyometria, poor smears, and problems of interpretation present additional difficulties.

Ovarian carcinoma can occasionally be detected in vaginal smears when there is metastasis to the uterus or tubes (13, 14). In the presence of ascites, the possibility exists that fluid containing malignant cells may traverse the tubes into the uterine cavity. Adenocarcinoma of the fallopian tube can also at times be detected by this technique. Such circumstances, however, are unusual, and the vaginal smear is not to be relied upon for their diagnosis.

Sarcoma of the endometrium (14) can apparently be diagnosed with a fair degree of accuracy. The number of cases thus far reported have necessarily been few because of its relative infrequency.

Carcinoma of the vulva is difficult to diagnose by the smear technique. This may well be due to the drying effect from constant exposure of the lesion to the atmosphere. Cuyler reported a 21.5 % error (11). In our small series of 5 cases, 1 was positive, 2 suspicious, and 2 negative.

The subject of "potential malignancy" has complex ramifications. A few comments, however, may be made on the association of atypical cervical lesions with the finding of dyskaryotic cells on vaginal smear. The term dyskaryosis (15) has been applied to those nuclear changes which are sufficiently atypical to suggest the possibility of malignant origin. When dyskaryotic cells accompany obviously malignant cells within the slide, no problem is presented. On the other hand, when found alone, their interpretation presents a problem. In 2000 gynecological cases studied by vaginal smears by us (16), there were 12 instances in which a purely dyskaryotic type of smear were found. Biopsy revealed conspicuous cervical cell atypism beyond that ordinarily seen. These cases were then followed by repeated vaginal smears and cervical biopsy. In one instance a positive smear for carcinoma was found two years later, and cervical biopsy at this time revealed an immature squamous cell carcinoma. In two other instances, in the course of one and one half years, both dyskaryotic smears and atypical biopsies were no longer found. In the remaining nine cases the condition remained unchanged in subsequent smears or biopsies.

Final conclusion could not be drawn from a study of 2000 vaginal smears. However, the findings indicate that one of the twelve women manifesting dyskaryosis in vaginal smears and atypism in cervical biopsy developed squamous cell carcinoma. These patients should be meticulously followed with repeated smears and multiple biopsies for many years to come.

Any critical survey must weigh the effects of a variable but ever present percentage of false positives or false negatives. Two main difficulties contribute to this; problems related to the preparation of smears, and to their evaluation. Smears cannot be made carelessly. Though the technique is extremely simple, certain rules must be followed:

1. Clean slides are selected, and thin spreads made in a gentle fashion. A thick glob of secretion will not permit accurate delineation of cellular abnormalities.

2. The specimen should not be allowed to dry, but dropped immediately into a jar of ether-alcohol.

3. Water or lubricating jelly should not be permitted to come in contact with the surface to be smeared.

4. Thorough contact by the Ayre spatula (17) with the cervix and endocervical canal is advised.

5. At least one slide containing a spread obtained by endometrial and endocervical aspiration should be included.

6. It is apparent that in a patient who is bleeding actively, mere dilution may mask the presence of a few exfoliated malignant cells.

7. The patient should be forewarned that a douche must not be taken beforehand.

The percentage of false positive reactions were estimated to be about 6% eight and nine years ago. Heynes in 1952 (18), and Graham in 1950 (19) reported that in patients without cancer their percentages of false positive reactions were as low as 0.26% to 0.04%. With increasing experience today, 1% to 1.5% false

positives in the hands of a good routine laboratory may be an anticipated high average. Therefore, since the number of false positives are so low a positive smear must be considered evidence of malignancy unless repeated and painstaking investigation proves otherwise.

False negative reports have a somewhat different significance. Several factors contribute to this:

1. The degree of desquamation of cancer cells is variable.
2. In necrotic lesions, secondary infection may destroy the exfoliated cells by lysis.
3. The omission through error of direct contact with the lesion or in some cases the failure to carry out aspiration technique add further obstacles.
4. And finally, the experience, astuteness, and persistence of the Cytologist cannot be disregarded.

At this time, one may expect on the basis of accumulated statistics, 95% of cervical carcinoma (20) and 83% of endometrial carcinoma to be properly diagnosed by the Papanicolaou smear.

The criticism has been raised that physicians are seeing increasing numbers of psychoneurotic women who plague their offices with requests for "the cancer test" without realization that it is applicable only to certain restricted types of lesions. The publicity given to the early detection of cancer in women has been done with full realization of the probable adverse effect on the hypochondriacal patient. She will require re-assurance and guidance. Suffice to say that the number of lives saved more than nullifies the increased anxiety engendered.

Graham (21) reported a series of 181 cases of squamous cell carcinoma of the cervix in which the initial biopsy was found to be correct in 91.2% of cases, and the initial vaginal smear correct in 92.3%. This is not intended to imply that the smear replaces the biopsy as a diagnostic method. One should complement the other. This is indicated by the fact that in the above mentioned series the use of both methods combined corroborated the diagnosis in 98.3% of the cases. It is obvious that in a small cervical lesion, a single biopsy may not be taken at the proper site, while the desquamated vaginal contents may well contain cells from all regions of the cervix.

One may say that a positive smear is considered presumptive evidence of a malignant lesion, which, however, requires further confirmation by cervical biopsy or curettage. A negative smear must be viewed with more skepticism, and in the presence of suspicious signs or symptoms should not be a deterrent to biopsy or curettage.

As the method is more widely tested, the accumulated observations of experienced cytologists and pathologists will further improve its diagnostic value. Silver (22) and fluorescent (23) stains are now being tried to determine if they are an improvement over the present stain. The photoelectric cell, in an attempt to reduce the factor of human error, is being experimented with as an aid in spotting the cancer cell in the stained smear. The Papanicolaou test is also used after radiotherapy (24, 25) as a prognostic aid in determining the response of the treated lesion; it also aids in the detection of local recurrences. In addition,

the Papanicolaou smear has been employed advantageously in sterility (28) and endocrinologic (26, 27) investigations. In those cases where estrogens have been administered postmenopausally, and bleeding has been induced, an unnecessary curettage may often be avoided by the cytological findings of the abnormal high cornified cells with a negative smear.

In conclusion, we would like to emphasize the fact that the smear method is morphologically sound, and that its usefulness in the diagnosis of malignancy in the female genital tract has been amply demonstrated. In many cases where typical cancer cells cannot be recognized, enough suspicion is aroused by abnormal findings to advise repeated smears or curettment and biopsy. As a short, simple, and inexpensive test, and one that can be repeated without inconvenience to the patient, it is particularly adapted to the screening of a large number of women, as in a cancer detection clinic.

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# ELEVATIONS IN TEMPERATURE OF JOINT, MUSCLE AND SKIN, FOLLOWING INJECTION OF PRISCOLINE INTRA- ARTERIALY

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The presence of a vasospastic component in rheumatoid arthritis and degenerative joint disease (osteoarthritis), initiated the investigation of priscoline (2, benzyl-imidazoline-hydrochloride)†, an adrenolytic and sympatholytic substance, as an anti-rheumatic agent (1). Oral and parenteral routes, not including intra-arterial, were utilized. The drug appeared to be of little or no value by the usual oral and parenteral routes. A wide dispersal of effect by such avenues was to be anticipated, and consequently no concentration upon a specific joint would be expected to occur. A direct intra-arterial route might more reasonably effect an intra-articular concentration of priscoline. This procedure has been investigated and the sometimes beneficial effect of intra-arterial priscoline upon degenerative joint disease was described recently (2). In a series of articles (3-6), Hollander and Horvath reported upon intra-articular temperature changes induced by various agents in normal subjects and patients with rheumatoid and osteoarthritis. Priscoline was one of the agents studied. Since their studies did not include the intra-arterial route, an investigation into the effect of intra-arterially injected priscoline upon the joint, muscle and skin temperatures seemed indicated.

## METHODS AND MATERIAL

The subjects were 9 healthy volunteers. Six were between 16 and 30 years of age. The other three were 39, 42, and 58 years respectively.

Intra-articular temperatures were recorded automatically by a Leeds-Northrup Micromax from iron constantin thermocouples incorporated in 19 gauge 2 inch needles with the thermocouple junction at the needle tip. The Micromax has 6 separate thermocouples registering one minute apart. Temperatures from each site consequently record at 6 minute intervals. Prior to each investigation, the subjects were not allowed to smoke for at least 2 hours, and each rested supinely for at least  $\frac{1}{2}$  hour. A thermocouple needle was then introduced into a knee joint from its medial aspect and supported carefully so that there was no pain or discomfort throughout the period of the observation. A similar thermocouple needle was inserted deep into the adjacent portion of the ipsilateral vastus medialis or lateralis muscle. One thermocouple registered room temperature. One thermocouple registered skin temperature from a site just lateral to the tibial

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† Priscoline was supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J.

tuberosity. (Only 4 thermocouples were used to record.) With a clinical thermometer, rectal temperatures were obtained at the start, and again after priscoline administration. After the thermocouples were in situ,  $\frac{1}{2}$  to 1 hour was allowed to elapse until temperatures at all sites remained steady. Following this, 25 mg. of priscoline were injected rapidly into the ipsilateral femoral artery. The temperatures were then recorded continuously for 1 to  $2\frac{1}{2}$  hours. In subject number 4, after  $\frac{1}{2}$  hour, an additional 25 mg. of priscoline were injected into the femoral artery. In three instances, normal saline was injected intra-arterially and observations recorded for  $\frac{1}{2}$  hour prior to injection of priscoline.

## RESULTS

Following the injection of normal saline intra-arterially, there was no noticeable change in temperatures in all 3 subjects. The intra-arterial injection of priscoline usually produced a distinct rise in temperature of skin, muscle and joint. The higher the initial temperature, the smaller the elevation following priscoline. The greatest rise in skin temperature was in subject 1 in whom a  $5.3^{\circ}\text{F}$ . increase occurred. The maximum joint and muscle changes of  $4.8^{\circ}\text{F}$ . and  $3.8^{\circ}\text{F}$ . respectively were observed in subject 7.

In subject 2, following priscoline the skin temperature rose only  $0.1^{\circ}\text{F}$ . despite a rise in the muscle of  $0.7^{\circ}\text{F}$ . and in the joint of  $2.3^{\circ}\text{F}$ . No elevation of muscle temperature was obtained in subjects 1 and 3, and in subject 9 only  $0.2^{\circ}\text{F}$ . increase was observed. No elevation of joint temperature developed in subject 3 and only  $0.3^{\circ}\text{F}$ . in subject 9. In all the subjects there was no observed change in rectal temperatures, and room temperature fluctuated only within  $0.7^{\circ}\text{F}$ . Subjective responses to priscoline injected into the femoral artery have been described previously (2). Untoward side-reactions were not observed.

Table I indicates the initial and the maximum temperature in each subject. Figure 1 presents the data in subject 7.

TABLE I

NO.	SEX	AGE	ROOM TEMP.	INTRA-ARTICULAR TEMP. (deg. F.)		MUSCLE TEMP. (deg. F.)		SKIN TEMP. (deg. F.)	
				Baseline	After intra-arterial Priscoline	Baseline	After intra-arterial Priscoline	Baseline	After intra-arterial Priscoline
1	M	58	81.5	93.2	95.0	98.2	98.2	90.0	95.3
2	M	17	82	93.9	96.2	96.8	97.5	93.1	93.2
3	M	39	80	98.8	98.8	98.4	98.4	90.2	93.0
4	M	42	84.5	95.1	97.0	93.3	95.5	93.0	96.2
				97.0	98.1	95.5	97.5	95.8	96.2
5	M	26	83	94.8	96.8	97.1	99.9	92.5	96.4
6	M	16	83	97.0	98.6	98.5	99.4	91.3	92.1
7	M	30	81.5	93.2	98.0	95.0	98.8	89.3	94.2
8	F	28	81.5	96.0	99.1	98.0	99.5	90.1	93.8
9	M	17	88.5	98.2	98.5	99.0	99.2	94.0	95.0

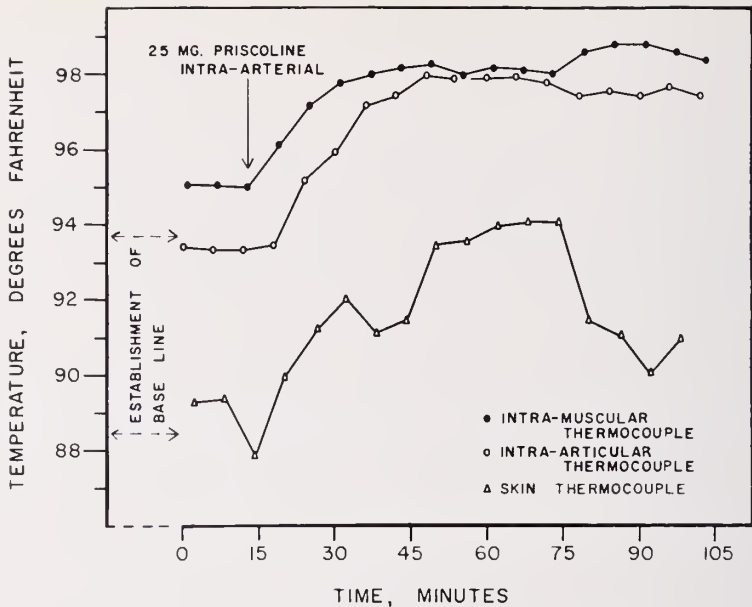


FIG. 1.

## DISCUSSION

There has been a general tendency to regard priscoline and similar drugs to be of dubious value in producing increased blood flow in the deep tissues (7). It is held that by intra-arterial injection priscoline will, in the main, produce an increase in blood supply to the skin. The suggested mechanism is a diversion of blood from the muscles and associated structures.

As demonstrated in this report, 25 mg. of priscoline effected a distinct rise in skin, muscle and joint temperature in 7 of the 9 cases. Elevation of intra-articular and muscle temperature did not occur in 2 cases where the initial reading was equivalent to body temperature. In subjects 2 and 4 (in the latter following a second injection of 25 mg. of priscoline), negligible increases in skin temperature ( $0.1^{\circ}\text{F.}$  and  $0.4^{\circ}\text{F.}$ ) were observed; and clearly higher joint ( $2.3^{\circ}\text{F.}$  and  $1.1^{\circ}\text{F.}$ ) and muscle ( $0.7^{\circ}\text{F.}$  and  $2.0^{\circ}\text{F.}$ ) elevations were noted. This is contrary to the usually accepted diversion of blood flow. (It must be noted that in subject 4, a  $3.2^{\circ}\text{F.}$  increase in skin temperature had already occurred following the initial 25 mg. of priscoline.) It would appear that diversion of blood supply to a part by means of vasodilating drugs need not flow always from deep tissues to the skin. The implication is that structures such as joints and muscles can be affected and their blood supply appreciably increased by drugs provided they are administered intra-arterially.

A recent Bulletin on Rheumatic Diseases (8) mentioned arterio-venous anastomoses in joints apparently acting as shunt mechanisms and directing blood flow to or away from capillary networks. It is conceivable that intra-arterial priscoline and similar autonomic system agents may increase the blood supply in and about a joint by activating such a mechanism.

It has been demonstrated in these experiments that in normal joints a distinct rise in temperature may be expected following the administration of priscoline intra-arterially. Simultaneous, though not necessarily similar, elevations are produced in the adjacent muscle and overlying skin. The direct, and thereby concentrated, application of priscoline to the joint by intra-arterial administration (as against the wide dissipation of its effect by other routes) probably accounts for the temperature alterations. It has been noted above that higher initial temperatures at all sites generally forecast a smaller elevation after priscoline was injected. It may be that lower basal temperatures would produce a wider range of increases. Also, larger doses of priscoline might effect a greater rise.

#### SUMMARY AND CONCLUSIONS

Following the femoral intra-arterial administration of priscoline, simultaneous skin, muscle and intra-articular temperatures were determined in the ipsilateral knee in 9 normal subjects.

In 7 of the 9, distinct skin, muscle and intra-articular temperature elevations were noted. In the remaining 2 subjects, the initial joint and muscle temperatures were already over 98°F. and a further increase was probably precluded.

In 3 of these subjects, normal saline was initially injected intra-arterially. In no instance was there an alteration in temperature.

It is suggested that vasodilating drugs such as priscoline do not necessarily divert blood flow from deep structures to the skin.

Studying the temperature changes reported above, it is conceivable that the injection of a vasodilating drug intra-arterially produces a direct concentration in and about a joint and effectively increases local blood flow.

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# *Important Notice*

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THE JOURNAL OF  
THE MOUNT SINAI HOSPITAL



## *In Memoriam*

CLARENCE P. OBERNDORF, M.D.

1882-1954

To the list of the illustrious dead of The Mount Sinai Hospital has been added the name of Dr. Clarence P. Oberndorf—first consulting Psychiatrist to the Hospital.

Born in New York City in 1882, he received his B.A. degree in 1904 and his M.D. degree in 1906 from Cornell University. During his internship at Bellevue Hospital he attracted the attention of a leading neurologist, Dr. Charles L. Dana who stimulated his interest in nervous and mental disorders. He continued his post-graduate studies in Europe under Theodor Ziehen and Emil Kraepelin. On his return, he joined the staff of Manhattan State Hospital where he participated actively in the early application of Sigmund Freud's theories in the understanding of the psychoses. In 1909 he became one of the first psychoanalysts in private practice in the United States, and although an instructor in Neurology at Cornell Medical School, he gave most of his attention to Psychiatry. In 1921-1922 he returned to Europe for a personal analysis with Freud. At The Mount Sinai Hospital, which he joined in 1913, he served as Associate Psychiatrist (1925-1939) and as Consulting Psychiatrist (1953-1954). He was Clinical Professor of Psychiatry at Columbia University (1936-1953).

In 1913 Dr. Oberndorf organized a psychiatric clinic at The Mount Sinai Hospital—one of the first of its kind in a general hospital. He attracted to it young psychiatrists with an interest in the psychoanalytic approach. Many psychiatrists who later established enviable careers in psychiatry and psychoanalysis had their early experience in psychotherapy in the clinic. The senior members of the clinic also came to serve as consultants on the wards for patients whose clinical pictures appeared to have etiological or secondary psychic factors. This involved pioneering work, for in addition to the patients investigated, it alerted the physicians to the potency of emotional factors in human ailments. At a time when psychoanalysis in the United States was still not established Dr. Oberndorf skillfully and patiently introduced the non-psychiatrist on the staff to psychoanalytic principles both in the understanding and management of patients. He also introduced occupational therapy for patients in the psychiatric clinic. In this and many other ways Dr. Oberndorf laid the foundation for the present large and active psychiatric service. His point of view was clinical understanding of the patient, solicitude for his welfare, and a consistent effort to alter the abnormal elements. Even in long and tedious investigations he always kept in mind the reasons which brought the patient to him. Dr. Oberndorf attained an important place as a therapist and an author in American and international psychoanalysis, but he never lost his human touch and warmth.

Dr. Oberndorf's experience at The Mount Sinai Hospital led him to help



CLARENCE P. OBERNDORF

establish the Committee on Mental Health among Jews, of which the now expanding Hillside Hospital is an example. He also organized a psychiatric service at what is now the Pleasantville Cottage School of the New York Jewish Child Care Association.

Dr. Oberndorf had an impressive personality. He made many friends and enjoyed maintaining contact with them. He had the happy faculty of putting people at ease. His love for people and delight in conversation made it easy for others—no matter of what age or status—to benefit from his advice. His informal manner always stimulated exchange of opinions. It was always a special pleasure for younger colleagues to talk things over with "Oby". One could always rely on his wide experience and one did not have to fear to venture with new ideas because "Oby" himself never gave up the search for new ways and means of handling psychic disturbances.

He wrote more than 120 scientific papers on a wide variety of psychiatric and psychoanalytic subjects. Not only had he studied and written extensively on the phenomena of unreality and depersonalization but he had great ability in depicting clinical histories and was always welcomed to present such material or to utilize his extensive clinical experience in discussion of the work of others. He was for years Associate Editor of the *International Journal of Psychoanalysis* and of the *American Journal of Psychiatry*. In addition he was the author of *The Psychiatric Novels of Oliver Wendell Holmes* a study of psychiatric thinking in the portrayal of characters in the pre-Freudian era; *Which Way Out*, a utilization in story-form of psychiatric principles, and *A History of Psychoanalysis in America*.

Dr. Oberndorf's recognized leadership is further attested by his election to the presidency of The New York Psychoanalytic Society, The New York Society for Clinical Psychiatry, The Schilder Society, The American Psychoanalytical Association and the American Psychopathological Association. He was also Chairman of the Section of Neurology and Psychiatry of the New York Academy of Medicine.

Dr. Oberndorf was motivated by a strong therapeutic zeal, always on the alert to evaluate the results of therapy. As an interne at Bellevue he was shocked by the brutal treatment of patients with functional disorders. He was determined to search for more rational methods, and early in his career, joined the psychoanalytic movement. Later as a successful analyst, his therapeutic zeal was again challenged by the failure of psychoanalysis in cases where it was supposed to succeed, and Dr. Oberndorf spent years in investigating this problem and alerting others to the study of unsuccessful cases. He did not mean to deny the potentialities of Psychoanalysis. He often said: "I have had my successes but I want to investigate the failures."

Shortly before his death, the Hospital honored Dr. Oberndorf by establishing the Clarence P. Oberndorf Visiting Psychiatrist Program.

PAUL GOOLKER, M.D.  
for the EDITORIAL BOARD



## *In Memoriam*

HENRY MINSKY

1895-1954

The hospital, the city, the world are made poorer by the sudden passing of Henry Minsky, whose tireless, painstaking work, endless compassion, and utter selflessness, made him an outstanding ophthalmologist, friend, teacher, parent and husband.

Born in New York in 1895, he chose medicine as a career in his earliest days and never swerved from this goal. After completion of his pre-medical education at DeWitt Clinton High School and Columbia College, he entered the College of Physicians and Surgeons in 1915. Here he soon became interested in ophthalmology, largely as a result of association with Dr. Oscar Diem there. The latter had been a pupil of Dr. Ernst Fuchs in Vienna and communicated his enthusiasm to the young medical student. During much of his medical school career Dr. Minsky spent the hours of 6 to 8 AM studying ophthalmology with Dr. Diem before travelling to school for his regular classes. After his graduation in 1919 and internship at Lebanon Hospital, he and Dr. Diem accompanied Dr. Fuchs in a lecture tour around the country, taking notes which were later published as "Notes and Remarks on Prof. Fuchs' Lectures."

He then spent several years of preceptorship, first with Dr. Diem and then with Dr. Charles May, before opening his own office. In spite of an extremely busy practice he found time for hospital work, research, and many outside interests. He was actively associated with the New York Eye and Ear Infirmary, and Harlem and Hillside Hospitals; later he was Consulting Ophthalmologist at all of these, as well as Norwalk General Hospital in Connecticut and Maimonides Hospital in Liberty, N. Y. He was a Fellow of the American College of Surgeons, the New York Academy of Medicine, and the American Academy of Ophthalmology and Otolaryngology, and a member of the New York Society for Clinical Ophthalmology, the Brooklyn Ophthalmological Society, the Pan-American Medical Association, the New York Plastic Surgery Society and the American Medical Association, as well as a past president of the Metropolitan Medical Society.

His most active hospital work was at the Mount Sinai Hospital, where he started as clinical assistant in 1924, gradually rose to become Chief in 1947. Under his direction the service was considerably enlarged and both clinical and research activity vigorously encouraged. He felt keenly that knowledge should be passed along, and spent much of his effort in expanding the teaching program. He organized two symposia on "Recent Advances in Ophthalmology" which were given by members of many of the hospital services and departments, primarily for ophthalmologists returning from the Army who wished to be brought up to date in their specialty. He taught several courses himself, and encouraged teaching by others. In recognition of all this, he was made Associate Clinical Professor of Ophthalmology at Columbia University.





HENRY MINSKY

His investigative work covers a wide range of subjects. He was extremely interested in the detailed anatomy of the lens suspension and its relation to the choroid and vitreous, introducing the concept of a "Zonular Chamber" and emphasizing its importance in the pathogenesis and management of glaucoma and of retinal detachment. He devised a method of converting the ophthalmoscope into a pocket slit-lamp which is widely used at the bedside. His method of surgical repair of recent lid lacerations, because of its simplicity and effectiveness, has almost universally replaced older methods. His passion for careful and systematic examination has been communicated to innumerable students, and his system of recording findings by means of consecutive diagrams has become widely known (as "Minsky's Circles"). About 20 years ago, he became interested in the fundus changes in hypertension. His careful observations have recently been presented in the posthumously published paper "Correlation of Ocular Changes in Essential Hypertension with Diastolic Blood Pressure."

Throughout his practice, he insisted on viewing the patient as a whole, not merely as a diseased eye. This ability and his intuition about people led to his being the focus of a wide circle of personal friends and neighbors, who looked to him as a combination of sage, doctor, and adviser, and to many of whom, related or not, he was "Daddy Minsky." He also had time for numerous relaxing pursuits. Most loved, and best known, was his painting. He received recognition on numerous occasions for his excellent oils and water-colors. He was also an avid musician, playing the piano, studying theory, and composing several piano and small instrumental works. He devoted considerable attention to his stamp collection, and was also interested in gardening, tropical fish, and chess. He was an active member of the Riverdale community, where he lived for twenty years.

While he will be remembered by his family as a husband, father, brother or son, by his associates as a teacher and guide, by his patients as an excellent doctor and by his neighbors as an inspiring leader, he will be remembered foremost by all of us as a friend.

Dr. Minsky is survived by his widow, Fanny, his children, Charlotte, Ruth, and Marvin, his father, Jacob, his sisters, Mrs. Sophie Jarvis, Mrs. Flora Mermelstein and Mrs. Alice Abrams, and his brother, Dr. Arthur Minsky.

DR. ALAN H. BARNERT, M.D.  
*for the Editorial Board*



## THERAPEUTIC ABORTION: THE DOCTOR'S DILEMMA

ALAN F. GUTTMACHER, M.D.\*

There is no facet of modern medicine to which the Shavian title applies more aptly than therapeutic abortion. The topic is complicated by medical uncertainties and human contradictions, by ethical principles and regional mores. What is the law, how leniently may it be interpreted? Should social and economic factors play a part in assessing medical indications? Is there an accepted legitimate incidence for the operation? In most instances, should sterilization be coupled with it? What is the hospital's role in the problem? What is the doctor's role?

I shall give answers to these questions, obviously personal answers, for in so contested a field no physician can frame replies which speak for the whole medical profession or even one segment. Then I shall summarize our experience with therapeutic abortion at Mt. Sinai since the inception of its Obstetrical Service, seventeen months ago.

The social anthropologist tells us that man's first attempt to control the size of his family was by infanticide. Yet abortion must also be very antique, for we find reference to it in the earliest medical records extant (1). A Chinese herbal written nearly 5000 years ago lists mercury as an effective abortifacient. Then too the first Egyptian medical papyri, the Kahun and the Ebers, give prescriptions for producing abortion. In the pages of the Hippocratic corpus written about 450 B.C. one finds the same conflicts and contradictions which characterize the problem of induced abortion today. The Hippocratic oath sanctimoniously forswears the production of abortion, yet we read in one of the case histories that a high priced musical entertainer came to the great seer complaining of inconvenient pregnancy. He advised that she leap into the air seven times with such vigor that her heels touch her buttocks. This she did and the conceptus "fell onto the ground with a plop" (2). I rather like this passage; it makes the father of medicine sound human:—susceptible to a well tuned harp, plus probably a well turned ankle.

The philosophers of ancient Greece favored the interruption of pregnancy on social and economic grounds. Aristotle said: "If it should happen among married people that a woman who already had the prescribed number of children became pregnant, then before she felt the life, the child should be driven from her." Plato recommended the obligatory abortion of every woman who conceived after the fortieth year (1).

Soranus, famous medical author and gynecologist of Rome during the reigns of Trajan and Hadrian, wrote of both therapeutic abortion and contraception.

Rome in 130 A.D. wrestled with the dilemma of the abortion problem much like New York in 1954. I quote from Soranus (3):

"But a controversy has arisen. For one party banishes abortives, citing the testimony of Hippocrates who says: 'I will give to no one an abortive.' The

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other party prescribes abortives, but with discrimination, that is, they do not prescribe them when a person wishes to destroy the fetus because of adultery or out of consideration for youthful beauty; but only to prevent future danger in parturition: if the uterus is small and not capable of accommodating the complete development, or if the uterus at its orifice has knobby swellings and fissures."

Legal enactments to prohibit abortion were foreign to most earlier cultures; this was the case in classic Greece and Rome. Even though there was debate between physicians about its employment, there was no legal statute prohibiting it. In China there was no thought given to even its impropriety until the late nineteenth-century.

Unequivocal moral and legal antipathy to abortion originated with the Hebrews, who were exhorted by God "to be fruitful and multiply." According to Josephus women who practiced abortion were severely punished by Jewish law. This attitude toward abortion was taken over unmodified from Judaism by Christianity. St. Augustine in about the year 400 classified abortion as murder. The Church Council of Ancyra excluded the guilty mother from taking the sacraments until the hour of her death. The attitude that therapeutic abortion is never justified no matter how dire the medical necessity, remains as unmitigated by the Catholic Church today as it was 1500 years ago.

The fact that the Roman Church declares any type of induced abortion to be murder does not make it so. Eastman in the *Obstetrical and Gynecological Survey* of April 1953 (4) makes an erudite comment upon this. He wrote:

"Whether judged by Webster's International Dictionary or by any textbook of criminal law, this usage of the word 'murder' is incorrect. Both these sources define murder in the same way as follows: 'Murder is the unlawful killing of a human being with malice aforethought, expressed or implied.' The distinguishing characteristic of murder is malice aforethought. When it exists the homicide is always murder. When it does not exist, the homicide cannot be murder, but is either manslaughter, or excusable homicide.

"The law recognizes that homicide may sometimes be justifiable or excusable. In the latter category, homicide in self-defense is an example. Actually, the law does not even regard abortion as homicide but expressly states that 'the killing must be of a living human being and not of a child unborn.' Nevertheless, if therapeutic abortion is to be compared to any form of homicide, it would seem to be most nearly analogous to excusable homicide in self-defense on the basis that the fetus is destroyed in defense of the mother."

It was only after the firm establishment of the Protestant Movement that medically indicated interruption of pregnancy was given religious, ethical, and legal sanction. In most of the world this sanction is still reserved for women in whom the procedure is carried out to preserve life or health. In all other instances our civilization considers induced abortion a serious crime.

There have been three notable exceptions to this statement.

In 1920 the Russians liberalized abortion so completely that practically any pregnancy less than 12 weeks could be terminated in a state abortorium simply for the asking. In 1929 Genss published a report on 30,000 induced abortions done



in Moscow with only eleven patients febrile post-abortion and no deaths. By 1934, with the imminence of a second world war, Russia began an acute about face. Article after article was published about the fearful sequelae of legal abortion. Under cover of this barrage, in 1935 the Russians rescinded *in toto* the liberal abortion law of 1920.

The Scandinavian countries, notably Sweden, to a lesser extent Denmark and Finland, comprise the second exception (5). Sweden introduced a new abortion law in 1939, which was modified in 1946. The Scandinavian laws are motivated by the attempt to reduce the high incidence of illegal abortion, particularly common among married mothers of several children impregnated by their husbands. Social and economic reasons, as well as the vague concept of "general debility" were added to previously existing medical indications for pregnancy interruption. Finland's abortion law became operative as recently as July 1, 1950. In both Sweden and Denmark a board consisting of an obstetrician, internist, public health doctor, social worker, and jurist acts on each application. In Sweden, during the 12 year period 1939 to 1950, there were 27,000 legal abortions; in 1951, 6,328 legal abortions and 110,000 live births, a rate of "58 per 1000 parturients." Another way of expressing the 1951 figure is one legal abortion to every 17 babies. The Swedish board validated 84 per cent of its applications in 1951, rejecting 16 per cent. In 1950, 30.2 per cent were authorized for "disease or some bodily ailment, eugenic indications 9.2 per cent, humanitarian indications 0.3 per cent, general debility 50.7 per cent." The grounds for the remaining 9.7 per cent were not stated, probably economic.

When visiting Copenhagen in the summer of 1952, I discussed abortion and sterilization with Prof. Brandstrup, a member of the Danish Board. "General debility" usually means either gross multiparity or a very short interval between pregnancies. Dr. Brandstrup told me that the proportion of legal abortions to sterilizations is approximately ten to one; probably the reverse of the American figure. The Danes view legal abortion quite lightly since its effects are relatively transient; not so sterilization, since its effects are permanent.

It is the general impression that the liberalization of the abortion laws in Scandinavia has done disappointingly little in achieving their aim, the reduction in frequency of criminal abortion (5).

Japan is the third country since 1920 to liberalize its abortion laws. The current law was passed by the Japanese Diet in 1949 and amended in 1952 (6). Its primary aim is to diminish the natural rate of population increase by lowering the birth rate. Contraception is notoriously unpopular in Japan for it is not considered nice or decent for a married couple to use any birth control agent during coitus; this is reserved for a man and his concubine. Physicians in each prefectural district are designated by the Medical Association to carry out interruption of pregnancy at state expense if the woman voluntarily applies for it and her case fits the necessary qualifications.

The laws which guide the physician abortionist are very broad. A summary follows:

"(1) If the person or the spouse (marriage need not be proved, common law

cohabitation suffices) has mental disease, mental weakness, psychopathies, hereditary physical disease or hereditary deformity.

(2) If the person or the spouse has a blood relative within the fourth degree of consanguinity who has hereditary mental disease, hereditary mental weakness, hereditary psychopathies, hereditary physical disease or hereditary deformity.

(3) If the person in question is suffering from leprosy.

(4) If the health of mother is endangered by the continuation of pregnancy or by the delivery due to physical or economic reasons.

(5) If a female has conceived by violence or threat, or by having committed adultery while she was unable to resist or refuse."

The following figures, astounding as they may be, are supplied by The Welfare Ministry of Japan (6). Japanese vital statistics are considered by experts to be among the most accurate in the world.

	1949	1950	1951	1952	1953*
Legal abortions	246,104	489,111	638,350	805,524	1,065,950
Sterilizations	5,752	11,405	16,233	22,424	
Births	2,723,873	2,356,856	2,157,414	2,024,000	
Birth rate per 1000	33.1	28.3	25.6	23.6	
Death rate per 1000	11.6	11.9	9.9	9.1	

\* On the basis of the first six months.

Turning attention from the historical, cultural, and global let us concentrate on the practical legal problems we face today.

The United States has no Federal Abortion law, each state having its own which varies considerably from state to state (7). On the other hand, England has a single law which operates for the whole of the British Isles. Such legal unification has significant advantages. First, it makes for more consistent administration; second, modifications of interpretation to affect all people are easier to implement. This is demonstrated by the famous English case of 1938. A fourteen year old girl was seized by three soldiers and raped and as a result impregnated. Alex Bourne, one of the most eminent obstetricians of Great Britain took the child to the public wards of St. Mary's Hospital, a non-Catholic institution, and aborted her without fee. To make a test case he then notified the Crown and asked to be arrested. He was tried under the Offences Against Person Act, Victoria, 1861. There was a famous three day trial. The Crown counsel charged that Bourne had broken the law which specified that interruption of pregnancy is only legal if done to "preserve the life of the mother." Bourne's defense was that the emotional life is just as much an integral part of life as its most physical aspects (1). The jury acquitted Bourne, which verdict has tended to liberalize the abortion law of England. If we were to attempt such liberalization here in the United States we would have to have 48 "Bournes" in 48 different States.

The law of New York reads: "A person who, with intent whereby to procure a miscarriage of a woman, unless the same is necessary to preserve the life of the woman, or of the child, with which she is pregnant is guilty of abortion, and is punishable by" etc. (7). At first glance there is an astounding incongruity.

How can one preserve the life of a child by causing its abortion? Apparently this was included to exonerate the physician who either performs a miniature cesarean section or induces labor in the child's behalf and yet delivers a fetus which does not survive. The real essence of the New York law is "*to preserve the life*" of the woman. Life and health are so intricately intertwined that when one preserves health he preserves the outlook for life as well. Therefore when pregnancy is terminated because its continuance is likely to injure health, even though it is believed it will not immediately cause death, it is on sound legal grounds. However, in New York abortion for eugenic reasons is outside of the strict phrasing of the law. Despite the fact that this is known to the State's Attorney's office, abortion on eugenic grounds is so generally accepted by the medical profession that no legal difficulty occurs.

The doctor's dilemma lies in the phrase "preserving the life of the woman." Take, for example, a 22-year-old, Class 3 cardiac who had a baby two years before. The pregnancy caused enforced invalidism throughout its course. The patient is 8 weeks pregnant again. She is referred to the obstetrician by the internist for interruption of pregnancy. Such a case can be analyzed from two points of view. The patient was carried through pregnancy safely two years before and there is good likelihood that this can be done again. It is true that she will be forced to remain in bed virtually throughout the pregnancy and cannot take care of her child or family. Yet a second child is unlikely to cause her premature death. On the other hand, one can argue that hers is a valuable life. She already has a 2 year-old child, and a husband to whom she owes obligations in the form of motherly and wifely duties. Is it fair to compel her to give these up for nine months? Furthermore, with the severe degree of organic heart disease which she has, her life expectancy is relatively short, and will it not be shortened still further by the necessity of caring for two infant children instead of one? Moreover no physician nor group of physicians is gifted with the power of prophecy and can be certain that a Class 3 cardiac will go into failure during the course of pregnancy from which she cannot be brought out. Hospital A would certify such a patient for abortion, while hospital B, equally ethical, would decide against abortion. It is unlikely such utterly divergent courses of action are both correct. This is the doctor's dilemma.

Should social and economic factors play a part in assessing medical indications? Let us go back to the Class 3 cardiac. Would it make a difference in deciding to carry or abort the hypothetical patient whether she came from a four story walk-up in the slums of New York or a Park Avenue Apartment with an elevator? In the first instance, she obviously has to do all her own work, or disband her home. In the second instance, domestic help can easily be acquired. Then, too, should economic and social conditions alone, without the involvement of any medical problem, be the sole indication for interruption of pregnancy? Should we abort a 27 year old Puerto Rican who has had eight previous pregnancies with five children surviving and eight weeks in her ninth pregnancy? One child is in a mental institution as the result of healed tuberculous meningitis, a 9 year old boy is a truant from home and the other three offspring represent various types of

emotional problems. The husband earns \$25 a week as a baker's helper. The patient herself is anemic with a hemoglobin of 5.6 grams, and intestinal parasites which would make a perfect demonstration for an all-inclusive chapter on this condition in a book on parasitology. What is the sound and proper course for these two patients? Should the pregnancies continue or be interrupted? This is the doctor's dilemma.

Is there an accepted legitimate incidence for the operation? It is impossible to answer this categorically. It depends in part on the type of patient clientele. In a teaching institution to which problem cases are referred from a large surrounding area, the incidence of therapeutic abortion should theoretically be high. On the other hand, an institution serving only private patients of the upper protected social group, should have a relatively low incidence. When surveying the literature, one encounters inconceivable differences in incidences. Eastman reports one therapeutic abortion to every 65 deliveries in a 12 year period at the Johns Hopkins Hospital, while Cosgrove and Carter report an incidence of one therapeutic abortion to every 16,750 deliveries at the Margaret Hague Maternity in Jersey City (4). Most institutions report incidences closer to those of the Johns Hopkins (8, 9). Russel studied the incidence of therapeutic abortion in 61 California hospitals during 1950 (10). These 61 hospitals reported a total incidence of 301 therapeutic abortions in 75,715 deliveries, an overall incidence of one therapeutic abortion to every 251 deliveries. But even in this same state under the same law, there is variation of one abortion to every 52 deliveries in a private hospital to one in over 8,000 at the Los Angeles County Hospital.

Tietze recently reviewed the data from the Bureau of Records and Statistics of the New York City Department of Health (11). Over a five year period, from 1943 to 1947, he found that the incidence of therapeutic abortion had declined from one to 196 deliveries, to one in 213. Eastman writes that from 1927 to 1935 there was one abortion to every 55 deliveries at the Johns Hopkins Hospital; 1936 to 1947, one to every 65, and in 1952, one abortion to every 450 births in the same institution (4). The most recent survey of therapeutic abortion reports the experience of the University Hospital at Charlottesville, Virginia. Thornton shows that from 1941 to 1945 there was one abortion to every 85 deliveries; 1946 to 1950, one to 119, and for 1951 and 1952, one to 337. From the three previous studies it is apparent that the incidence of therapeutic abortion has declined sharply in the last 20 years, the decline being most acute during the past decade. Unquestionably this diminishing necessity for interruption of pregnancy is the result of therapeutic innovations in general medicine and surgery.

Also during the past two decades there has been extensive realignment of indications for therapeutic abortion. Several years ago the chief indication was pulmonary tuberculosis, with toxemia of pregnancy second (including all forms of hypertension, hyperemesis and acute liver atrophy). Cardiac disease was usually in third position. Nervous and mental diseases were inconspicuous on any list until relatively recently. Other less common conditions were pyelitis, fibroids, diabetes, exophthalmic goiter and cancer. In the 1950 California study, a quarter of the cases were aborted for nervous and mental diseases; one-fifth for toxemia



and hypertensive diseases; one-fifth for pulmonary disease, mainly tuberculosis, and less than one-tenth for cardiac disease.

In view of the foregoing, it is futile to use a general formula for determining the proper incidence of therapeutic abortion in 1954. The figure is so obviously affected by the type of clientele which populates a particular institution; and more so by the overall philosophy of its staff in regard to this problem.

As to the fourth query, "Should sterilization be coupled with therapeutic abortion in most instances?" if an organic lesion is involved it depends upon the prognosis for recovery. For example, if abortion is done because of a very acute tuberculosis with cavitation it would be unwise to sterilize at the same time since with modern chemotherapeutic agents and pulmonary surgery the patient may be sufficiently cured of tuberculosis so that future child-bearing would be safe. On the other hand, if the patient has an advanced rheumatic heart with mitral stenosis and insufficiency, carditis and history of failure, it would be wise to accompany abortion by sterilization since there is little likelihood of radical improvement. Yet if one were dealing with a pure mitral stenosis considered ideal for surgical correction, one could either abort without sterilization and carry out commissurotomy, allowing prompt reimpregnation, or continue pregnancy and perform the surgery during its course. If interruption of pregnancy is carried out for eugenic reasons, it is ordinarily accompanied by sterilization. For example, a woman who transmits hemophilia is unlikely to be relieved of her taint and in such a case abortion should be accompanied by sterilization. But if evacuation of the uterus is done because of early pregnancy rubella, it would be senseless to perform sterilization at the same time.

Until reading the Rosen current Anthology on Therapeutic Abortion I had thought many abortions done on psychiatric grounds should be accompanied by sterilization (1). However, several of its authors claim that it is therapeutically injurious to sterilize most women aborted for psychiatric reasons. Myers, in a chapter on sterilization writes, "The urge on the part of the surgeon for sterilization in these cases is often an expression of his reluctance to perform the abortion, his lack of understanding of the psychiatric implications, and his resentment toward the psychiatrist for putting him in this position." In another publication, Rosen writes (12) "sterilization presents one set of problems; therapeutic abortion, another. Psychiatrically, at least, we do not feel that the two must necessarily be combined. In fact, we feel that so far as some of the patients whom we have seen are concerned, the urge which resulted in their sterilization is to be deplored. All too frequently patients who require therapeutic abortion for emotional reasons are penalized by sterilization for being psychiatrically so seriously ill. These patients are not untreatable and should not be considered as such, even though the psychiatrist may not be able to help them during the two to three week physiological time limit with which he is confronted, if he sees them only during their pregnancy."

The fifth question I would ask is, "What is the hospital's role in the problem?" The mechanics for authorization of therapeutic abortion vary from hospital to hospital. Each institution has its own rules. These fall into four general patterns:



1, Consultation with one or two other physicians; 2, Review and decision by the chief of the obstetrical and gynecological service; 3, Review and decision by the chief of staff or the medical director of the institution, and 4, Review and decision by a therapeutic abortion committee. This last is gaining recognition, and in all likelihood will become standard procedure in another decade. According to Russel, it was the system of choice in 11 per cent of 61 hospitals in California in 1950 (10).

The abortion board system was introduced at the Mount Sinai Hospital in 1952 when the institution inaugurated its obstetrical service. The Director of the Gynecological and Obstetrical Service is permanent Chairman of the Committee, the other members being one senior physician from the Departments of Medicine, Surgery, Neuropsychiatry and Pediatrics. The Board meets once a week at a stated hour if a case is pending. No case is considered unless the staff obstetrician-gynecologist desiring to perform the abortion presents affirmative letters from two consultants in the medical field involved. Five copies of the letters must be filed at least 48 hours in advance of the Committee's meeting, so that each member may have an opportunity to study the problem. The obstetrician-gynecologist whose case it is and one of the two consultants who wrote a recommending letter must make themselves available at the Committee meeting to furnish additional information if desired. Also if the Chairman feels that some expert from another department, hematology or radiotherapy for instance, will be helpful in arriving at a proper decision, this specialist is requested to attend as a non-voting member. The case is carefully discussed and if one of the five Committee members oppose therapeutic interruption, the procedure is disallowed. No termination of pregnancy may be carried out in any of the operating rooms of the Mt. Sinai Hospital unless an affirmative decision of the Abortion Committee has been previously filed with the Director's office.

It has been generally shown, wherever the board system has been introduced, that a material reduction in the number of requests for therapeutic interruption occurs since cases of questionable merit have little likelihood of being accredited for operation. No system to handle therapeutic abortion is ideal, but the board system has the advantage of consultation among several senior physicians and does not depend upon the views of one or two who frequently may have personal interests in affirmative decisions.

There are medical readers I am sure who object to an abortion board for the very reason I praise it, because it tends to reduce both the requests and the abortions done at the hospital which employs it. The physicians with no hospital administrative responsibility for the certification and selection of cases for therapeutic abortion advocate the operation far more freely than those who do. Why is this? A liberal conscientious hospital director, or chief of an obstetrical service, may chide against the restrictions of a rigorous, outmoded state statute but since he is entrusted to its administration in his institution he will perform his task according to its dictates. This responsibility is inherent in his position. By thus cleaving closely to the letter of the law he feels at liberty occasionally, without injuring the reputation of the service, to veer from the statute's strict legalistic

interpretations and to encompass the law's spirit. An example would be the occasional inclusion of eugenic indications for pregnancy termination. Unrestricted therapeutic abortion leads to loose medical thinking. Flouting the abortion law also acts as a springboard for unorthodox, borderline medical ethical practices.

Actually a moderate proportion of the abortions agreed to even by an abortion committee are somewhat in the quasi-legal group. The truly legal abortions, in which the procedure is absolutely essential to preserve a woman's life are relatively few. If one should apply this yardstick, and this yardstick alone to each case, it is unlikely that more than one abortion in 500 or 1000 pregnancies is technically legal. Legitimate hospitals accept in addition some cases in a quasi-legal bracket, but only accept those of crying necessity. The greater the incidence of abortion in a given institution the greater the proportion from the quasi-group, for the truly legal cases have a more or less constant incidence all over the country. I am not opposed either emotionally or intellectually to socio-economic indications for abortion but as long as I am chief of an obstetrical service, I am strongly against them as the sole indication while the present New York statute stands unmodified. As director of an obstetrical department, I believe it my duty and charge to carry out the rules for abortion accurately and yet justly. No difference should be made between private and ward patients, and no difference between the patients of the senior staff man or the most junior. Certainly, I would have no quarrel if an abortion is refused at the Mount Sinai Hospital and the private doctor seeks to have it done at some other institution. The therapeutic abortion committee of Mount Sinai has no jurisdiction over what is being done at other institutions. I have heard our rigid rules criticised on the basis that when patients are refused abortion they either end up in another institution or in the hands of an ill-prepared and dangerous illegal abortionist. I deprecate such an outcome as the latter, but feel it can not sway the judgment of an impartial and just board of physicians.

The sixth question I would ask is, "What is the doctor's role?" If a patient comes to the obstetrician-gynecologist asking for interruption of pregnancy, it is his responsibility to listen to the history and by whatever appropriate examinations or consultations necessary to make up his mind fully whether or not interruption is a medically justifiable procedure. I do not feel that the obstetrician-gynecologist is simply the patient's agent who presents her request for interruption of pregnancy without himself evaluating it. I think he should pass this request on to hospital authorities, whether Mount Sinai or some other institution, only if he is convinced of the wisdom of the request. If he thinks the procedure unjustified, it behooves the physician consulted to discuss the matter in great detail with the patient and to attempt to persuade her to his viewpoint. If he fails to do this he has no further responsibility in the case. Some cases cannot be simply decided, and if the doctor himself is uncertain it is wise to pass the problem to a consultant with the statement that help is needed in arriving at a proper decision.

After this long introduction, I shall summarize the work of the Abortion Com-

TABLE I

INDICATION	REQUESTS	TOTAL ABORTED	ABORTED ALONE	ABORTED AND STERILIZED	REJECTED
Psychiatric	19	15	12	3	4
Malignancy	5	5	4	1	0
Prev. breast ca.	2				
Prev. thyroid	2				
Malig. melanoma	1				
Rheumatic Cardiac Disease	2	2	0	2	0
Chronic Nephritis	2	2	1	1	0
Nephrectomy, history of infect. remaining kidney	1	0	0	0	1
Eye	2				
Unil. ret. thromb. prev. preg.	1	1	0	1	0
Unil. detached retina normal preg. since	1	0	0	0	1
Multiple sclerosis	1	0	0	0	1
Hodgkins	1	0	0	0	1
Bronchiectasis-tbc.	1	1	0	1	0
Cong. amput. both legs, scolosis	1	1	0	1	0
Rubella	5	4	4	0	1
Total	40	31	21	10	9

mittee of the Mount Sinai Hospital during its first 17 months of existence, November, 1952 to April, 1954. During this period the obstetrical service at the Mount Sinai Hospital delivered 3,999 women. At the same time, the Abortion Committee authorized interruption for 31 pregnancies, an incidence of one abortion to every 129 deliveries. Forty requests were presented to the committee, 9 rejected and 31 validated. In other words  $77\frac{1}{2}$  per cent of the interruptions requested were granted. Thirty-three of the requests involved private patients, seven of these were rejected, a rejection rate of 21 per cent. There were seven applications for clinic patients and two rejections, a rejection rate of 30 per cent. Since the delivery ratio of private to clinic patients is two to one, and since the requests were in the ratio of almost five to one, it is obvious that therapeutic abortion is requested more frequently in the private group. Neither the forty requests nor the low rejection rate are true indices of the demand for therapeutic abortion at Mount Sinai, nor of the temper of the Committee. A large number of cases which almost certainly would have been turned down never got as far as the Committee. Many physicians are discouraged by telephone conversation or corridor consultation with a single Committee member. Within the past 72 hours, I have been asked how I would feel about two interruptions, one a depressed woman in her third illegitimate pregnancy, the other a spastic hemiplegic who is two months pregnant four months after a previous delivery. In both instances I gave an unofficial opinion that neither case met the Committee's criteria but strongly stated to each interrogator that he could present the patient if he desired. This "curb-stone" review of a case becomes the task of each Committee member several times a year, in my situation several times a month.

Table I lists the total number of cases considered for each indication, the number aborted, the number aborted with and without contemporaneous sterilization, and the number rejected. The five cases of rubella all had the infection before the 10th week of gestation. The case refused was on the grounds that no competent pediatrician or internist had seen the patient during her illness and the diagnosis remained medically unverified. The cases most difficult to decide are those presented on psychiatric grounds. It is common for a patient inconveniently pregnant to be depressed by the prospect of an unwanted child. Therefore the Committee remains unmoved by the psychiatrists' statements that a patient brought before it is depressed. On the other hand, if there has been previous history of actual psychiatric therapy for a major psychotic difficulty, and if it is thought that on the basis of the current pregnancy another major psychosis will result, the problem is quite different in scope. Also the Committee has to be convinced that the pregnancy and the patient's reaction to it represents a real threat to life from the viewpoint of possible suicide. The law is phrased "to preserve the life," and the only way that a psychiatric illness can really interfere with the life of a patient is by her taking her own life, motivated by the insoluble problem of pregnancy for which she finds no other solution than suicide. The existence of a psychosis in itself is not sufficient grounds for interruption of pregnancy. In psychiatric institutions, if patients become impregnated when furloughed home, therapeutic abortion is not done on return to the institution. The patient is carried through pregnancy and protected from harming herself during its course. There is little evidence that pregnancy in itself worsens a psychosis, by either intensifying it or rendering prognosis for full recovery less likely.

It is possible my discussion has failed to clarify the problem of therapeutic abortion for the reader. If so, there is little wonder, since it is not crystal clear in the mind of the author. For me, therapeutic abortion remains and gives promise of long remaining "the doctor's dilemma"

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# PANCREATITIS: A REVIEW<sup>1</sup>

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## INTRODUCTION

Within the past twenty years, our knowledge of pancreatic disease has been advanced by the contributions of the physiologist, the internist, and the surgeon. The mechanics of the external pancreatic secretion have been clarified and utilized in the development of tests of pancreatic function. The pathogenesis of acute pancreatitis is much better understood, thus making possible more rational treatment of this disorder, with resultant marked lowering of mortality. Improvements in the surgery of chronic pancreatitis and pancreatic neoplasm have produced improved response in a group of patients hitherto beyond therapeutic control.

Before discussing the clinical features of pancreatitis, a review of the physiological background of pancreatic secretion is in order. The mechanics of secretion are more complex than the original hormonal concept of Bayliss and Starling (1, 2), first introduced in 1902. Pancreatic flow is now known to be regulated by three factors (3): 1. Hormonal (1, 4), 2. Central Autonomic-Vagal (5, 6) and Sympathetic (7, 8), and 3. Peripheral Local Neurogenic Reflex (3). Of these, Thomas (3) is inclined to credit the first, or hormonal factor, as most important in homeostasis in the duodenum, i.e. maintaining alkalinity of the duodenum in order to provide an optimal medium for action of the pancreatic ferments. The vagal mechanism and the local duodeno-pancreatic sympathetic reflexes, Thomas believes (3), may be of greater significance in regulating pancreatic secretion during human digestion.

The hormone, secretin, of Bayliss and Starling is now known to be a complex which has been fractionated into 5 distinct components:

1. *secretin proper* (2)—which incites the flow of voluminous, thin, high buffering, low enzyme-containing pancreatic juice,
2. *pancreozymin* (4)—which stimulates the flow of a viscid, high enzyme, pancreatic secretion,
3. *hepatocrinin* (9)—which causes the elaboration of a thin, salt-poor, biliary flow,
4. *cholecystokin*in (10)—which induces contraction and emptying of the gall bladder, and
5. *enterocrinin* (11)—which stimulates the flow of the succus entericus.

The secretin complex is produced mainly in the duodenum and to a lesser extent in the upper small bowel under the influence of hydrochloric acid and various foodstuffs, especially fat, on the intestinal mucosa. The hormones are absorbed into the bloodstream and carried to the pancreas, liver, gall bladder, and jejunum where they exert their stimulatory effect, either directly as main-

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tained by Bayliss and Starling (1) or indirectly through the mediation of the vagal fibers as claimed by Pavlov (5).

Mellanby (12), in 1925, was able to show that secretin was responsible for the water and bicarbonate secretion of the pancreas and that vagal stimulation resulted mainly in the elaboration of enzyme. For a time, this observation bridged the gap between the proponents of the hormonal concept and the nervous concept of pancreatic secretion. This harmony was shattered by Harper and Raper (4) who isolated pancreozymin from the secretin complex and demonstrated that injection of this hormone into vagotomized animals resulted in marked stimulation of enzyme secretion. On the other hand, Thomas (3) has shown that vagal action potentiates the secretin and pancreozymin effects.

While the action of the vagus nerves in pancreatic secretion has, to some extent, been clarified by studies in patients before and after vagasection (13-15), the effect of the splanchnic nerves on pancreatic secretion has not been clearly defined (15). In the experimental animal, small decreases in pancreatic flow can be observed following sympathetic stimulation (7) but some augmentation may also be observed after splanchnic section (8). Kuntz and Richins have explained these findings by postulating that the effect of sympathetic stimulation on pancreatic secretion is a summation of motor and inhibitory actions on the gland superimposed upon the secretory changes produced by alterations in the blood supply to the pancreas (16, 17).

Pancreatic juice, as it appears in the duodenum, consists primarily of water, sodium bicarbonate, and digestive enzymes. Trypsinogen and chymotrypsinogen are the proteolytic enzymes of pancreatic secretion, which, when activated in the alkaline duodenal chyme, break proteins down to polypeptides and to amino acids, in which latter form they are absorbed. Pancreatic lipase converts fats and phospholipids to glycerol and fatty acids, which, in complexes with phosphates and bile salts, can be assimilated. The amylase of the pancreas is responsible for the degradation of starch and glycogen to disaccharides. Although these pancreatic enzymes play a major role in the digestion of foodstuffs, they are not absolutely essential to the maintenance of life. Patients have survived total pancreatectomy with some deleterious effects but these are not necessarily serious. Apparently digestion is carried on by the intestinal proteases, lipases, and diastases to a fairly satisfactory degree since these individuals can be kept in nutritional balance. Fat digestion seems to be the most impaired and large amounts of fat are lost in the stool unless fat is severely restricted in the diet.

#### PATHOGENESIS

Pancreatitis is a destructive process in which a constant factor is the passage of activated enzymes from the normal channels of the gland, its ducts, into the parenchymal tissue of the pancreas. The lipase and trypsin are responsible for digestion of fat and protein in and about the gland. The basic mechanism by which these enzymes escape and produce disease is still a subject of much discussion and controversy.

Pancreatitis may be produced by the injection of bile and other substances

under pressure into the pancreatic duct (18-20). It has usually been assumed that bile, *per se*, is the cause of the pathological process (21). However, Rich and Duff (20) have shown that it is the large volume and high pressure of injection which produce disruption of the pancreatic ducts and release of enzymes into the gland substance (20). This method of producing pancreatitis is the analogue of the common channel in human beings. Pancreatitis may occur when the ducts of Santorini and Wirsung are ligated and a maximal stimulus to pancreatic secretion is applied (22, 23). There occurs a rise in ductal pressure with a bursting of enzymes from the normal confines of the duct system into the gland and into the bloodstream (24). The latter pathway accounts for the characteristically elevated serum amylase values (24). Clinically this mode of genesis is encountered in the form of pancreatitis which occurs after a heavy meal (25) or after the ingestion of a large quantity of alcohol (26).

A more recently introduced means of inciting pancreatitis is the administration of ethionine (27-29). Ethionine is an amino acid antagonist of the essential amino acid methionine (27). Its administration in some way interferes with protein metabolism and results in vacuolization and degeneration of the acinar cells of the pancreas (28). The end result of continuous ingestion of the drug is pancreatic atrophy without the dynamic picture of acute pancreatitis as it is usually seen (29). It is possible that the pancreatitis of alcoholism and the pancreatic atrophy of kwashiorkor, ulcerative colitis, sprue, ileitis, and cirrhosis may be analogous to this form of the disease (26, 30-35). Pancreatitis may result after physical trauma to the abdomen and following surgical operation, notably subtotal gastrectomy, in which pancreatic ferments are released locally into and about the pancreas (36-39). In addition, in subtotal gastrectomy, Millbourn (40) has marshalled evidence to suggest that injury to the duct of Wirsung precedes the pancreatitis which occasionally follows this procedure.

Pancreatitis is the result of a chemical and autolytic process. It may be infective or non-infective. In the overwhelming majority of the cases of pancreatitis bacterial infection is not present at the beginning of the process, but superimposed infection of the necrotic tissue frequently leads to suppuration. This may explain the beneficial effects that have been reported from the use of aureomycin and other antibiotics in pancreatitis (41). The pancreatitis which occurs following mumps and in the course of scarlet fever, typhoid fever, and septicemias is bacterial from its inception (42).

#### ETIOLOGY

The literature is replete with reports of investigations and conjectures about the etiology of pancreatitis. Excellent summaries of these considerations have been prepared by Ravdin and Johnson (21), Dragstedt, Haymond, and Ellis (42), and Lewison (43). Four major theories have been advanced to explain the pathogenesis of pancreatitis:

1. The ampulla of Vater may be blocked by a calculus (44), by spasm of the sphincter (45-48), or by edema of the sphincter (26, 49, 50) so that a common channel is formed and the common bile duct communicates with the pancreatic

duct, thus permitting free flow of bile into the pancreatic duct with activation of pancreatic enzymes and resultant destruction of pancreatic tissue.

2. Bacteria may attack the pancreas by way of drainage from infection elsewhere in the body (42, 51).

3. Obstruction of the pancreatic duct at a time when activity of the gland is heightened may result in increased pressure within the ductal system and the passage of pancreatic juice from the ducts into the pancreatic parenchyma (52).

4. Specific pancreatic poisons such as alcohol (53-55) and ethionine (27-29) may injure the secreting cells and alter the "enzyme partition" (56) so that pancreatic ferments pass into the tissues and into the bloodstream.

The "common channel" theory was first propounded by Opie (57) who found a calculus impacted in the ampulla of Vater in a case of acute pancreatitis. Opie's paper and that of Bayliss and Starling, both published in the same year, stimulated the research which has done much to resolve the problems of pancreatic disease.

Numerous supporters and opponents have risen to the defense and denial of the common channel theory. To explain those cases in which no stone was found in the ampulla, Archibald (46) demonstrated experimentally that spasm of the ampullary muscle could produce the common channel. Later, Balo and Ballon (50) proved that edema of the mucosa could also account for the formation of the common channel and their work has been generally accepted. No one, however, has offered a satisfactory explanation for those cases in which the common duct and the pancreatic duct empty into the intestine at a considerable distance from each other, or for those cases in which pancreatitis was found to be limited to a small portion of the gland or to that portion drained by the duct of Santorini (58). Dragstedt (42), in 1934, came to the conclusion that the common channel theory probably accounted for about 60% of the cases of acute pancreatitis and that in about 10% of these a stone would be the inciting factor. He had no satisfactory explanation for the 40% of the cases in which no common channel could be demonstrated.

The anatomical evidence in favor of the common channel theory is the high incidence of common channel configurations in autopsy material. Mann and Giordano (59) found this incidence to be about 20% of 200 cases. Cameron and Noble (19) reported the findings in 354 dissections to show an incidence of 76% and Howard (60) discovered common channels in 54% in 150 autopsies. It has been argued that the existence of a common channel need not necessarily imply biliary reflux inasmuch as the pancreatic intraductal pressure is higher than the combined pressures exerted by the liver and gall bladder (59, 61, 62). The indications, by far, are in favor of pancreatic reflux into the biliary tract (61, 63). Indeed, despite repeated demonstrations of anatomical common channels with cholangiographic techniques (60, 64), there is only meagre direct pathological and chemical evidence of the presence of bile in the pancreatic tract (65). Hicken (65), in fact, questions whether the reflux of bile into the pancreatic ducts is an abnormal physiologic process.

Rich and Duff (20), in 1936, expressing dissatisfaction with the common

channel theory, showed experimentally that it was not bile, *per se*, which produced the lesion, but rather the pressure under which the bile was injected into the pancreatic ducts. They introduced india ink and colored Locke's solution into the accessory pancreatic duct and flooded the interstitial tissue. This resulted in acute pancreatitis. Their work corroborated the report of Mamm and Giordano (59) who showed that the quantity of bile (5–15 ml.) or other fluids injected into the pancreatic duct necessary to produce experimental pancreatitis is more than enough to rupture the ducts and infiltrate the pancreas with the injected fluid. Interpreting their experimental observations in the light of clinical experience, Rich and Duff concluded that the majority of cases of pancreatitis result from partial obstruction and escape of pancreatic juice into the gland. This sequence of events could occur during periods of increased pressure within the ductal system resulting from factors which increase the quantity of endogenous secretin, especially after a large meal or an alcoholic debauch (23, 66).

Rich and Duff, though not favorably disposed to the common channel theory, admitted that a gall stone impacted in the ampulla of Vater could obstruct the main pancreatic duct. On the other hand, these observers found metaplasia of the epithelium of the pancreatic duct obstructing and narrowing the ducts in 13 of 24 cases of acute hemorrhagic pancreatitis and in 18.6% of 150 consecutive autopsies in individuals over twenty-five years of age. The concept of metaplasia, though widely quoted in the literature and textbooks, has not gained wide acceptance because of the infrequency with which it can be demonstrated in postmortem cases of pancreatitis. In addition, Yotuyanagi found ductal metaplasia in 50% of normal pancreatic glands in autopsy material (67).

The theory of infectious pancreatitis is valid as regards bloodborne pathways and has been proved both experimentally (42, 68) and clinically, witness the incidence of acute pancreatitis in typhoid fever, scarlet fever, and mumps (69–72). Though direct drainage of infection from the lymphatics of a diseased gall bladder has been discarded as a pathway (73), internists have, for a long time, appreciated the coincidence of chronic gall bladder disease and acute pancreatitis, and, what is more important, the beneficial effect cholecystectomy may have upon chronic pancreatic disease (58). Over 70% of the reported cases of acute pancreatitis have been associated with biliary tract disease (58) and 50% of the patients have biliary tract stones (58). Cholelithiasis is six times more frequent in patients with pancreatitis than in control groups of autopsy material (51).

The association of alcoholism and pancreatitis has been repeatedly stressed since Friedreich's report in 1878 on the "drunkard's pancreas" (74). Fitz (75), Halsted (18), Opie (57) and others (33–35, 54, 76–80) wrote extensively concerning this association. Weiner and Tennant (81) reported acute alcoholism in 52% of 51 cases of acute pancreatitis and chronic alcoholism in 47% of 41 cases of chronic pancreatitis. Clark (82), Paxton and Payne (66), Bockus and Raffensperger (83), Comfort (84), and Edmondson (85) also reported on the high incidence of alcoholism in their series of patients with chronic pancreatitis. Carter (49) and Domzalski (86) noted a high incidence of elevated blood amylases in alcoholics admitted to city hospitals with a diagnosis of delirium tremens or acute



alcoholic gastritis. Their observations suggested that alcoholics suffer from repeated mild or subclinical attacks of acute pancreatitis, the cumulative effect of which results in chronic pancreatitis. Despite the inescapable conclusion that alcoholism, even in the absence of biliary tract disease, may be a direct cause of pancreatitis, the mechanism of this etiological relationship remains unproved. Egdahl (76) suggested that gastroenteritis produced by the alcohol might be responsible for the pancreatitis. Probst (55) believes that alcoholic pancreatitis may be a distinct entity differing in etiology from non-alcoholic pancreatitis. Myers (54) advanced the following possibilities: 1. that alcohol in the blood might stimulate or damage the pancreas directly, 2. that duodenal congestion might obstruct or infect the ducts, and 3. that persistent vomiting might cause regurgitation of duodenal contents into the pancreatic ducts. Dreiling and Richman (26), however, showed that intravenous alcohol did not stimulate the pancreatic flow. They noted no exacerbation of pancreatitis when alcohol was given intravenously to patients with known pancreatic inflammatory disease. Richman and Colp (52), basing their argument upon the clinical observation that acute pancreatitis often occurs after a large alcoholic intake, postulated that alcohol, coming into contact with the duodenal mucosa, would stimulate, within limits, quantities of secretin in proportion to the intensity of stimulus. Thus, following debauches, large amounts of pancreatic juice would be elaborated. Pancreatitis would result when there was excessive pancreatic flow against some resistance in the pancreatic duct system, e.g. stone, edema, metaplasia, etc. (66). Popper and Necheles (22) and Lium and Maddock (23) had supported this hypothesis by inducing pancreatitis in animals with ligated pancreatic ducts by means of the injection of mecholyl or secretin or by the ingestion of food.

Alcohol, when taken orally, is capable of stimulating pancreatic secretion both via the acid-secretin mechanism indirectly and by stimulating secretin in the duodenum (87). Brooks and Thomas (88), however, deny the latter action and attribute the entire effect of alcohol to its acid-forming properties. McGowan, Butsch, and Walters (47) have shown that HCl and alcohol, passing into the duodenum, are capable of producing spasm of the sphincter of Oddi. After large quantities of alcohol, edema of the duodenal mucosa and papilla of Vater may result. By these actions, then, alcohol may be capable of producing attacks of acute pancreatitis.

#### PATHOLOGY

The pathologic changes in pancreatitis are known to us, for the most part, as seen at autopsy or at operation. These changes usually represent the latter phases of the inflammatory process. However, recent experimental evidence has demonstrated the earliest response of the pancreas to injury. The underlying mechanism in the production of pancreatitis is the escape of enzymes into the interstitial tissue of the pancreas, and the earliest response of the gland to this injury is edema. Hallenbeck (88) has witnessed swelling and glassy induration of the gland within minutes after subjecting it to insult by injection of bile into the ducts. Edema may occur in any part or in the whole organ, the head being



most commonly affected. The area involved becomes pale, edematous, and indurated. Congestion of the vessels may not occur immediately but, if not, invariably develops as the disease progresses (90).

Microscopically, edema fluid is identified in the interlobular connective tissue and in the acini. Polymorphonuclear leukocytes and round cells are suspended in the fluid. In the majority of the cases, this inflammatory edema recedes spontaneously within ten to fourteen days with very little fibrosis (21). In a certain percentage of cases, the exact figure being unknown, the disease may progress to necrosis, hemorrhage and suppuration. It is easy to postulate that this progression may vary with the extent of the pathogenetic factors. If the hypersecretion-obstruction theory is accepted, one may assume that with heightened obstruction secondary to spasm, stone or edema, accompanied by increased secretion, pancreatic enzymes will induce a more severe response. The escape of the proteolytic enzyme, trypsinogen, into the tissues allows activation to trypsin, with the digestion of the protein structures. The result is necrosis and hemorrhage in those instances in which the blood vessel walls are attacked and the pancreas shows numerous soft, yellow, gray, black or red areas. Microscopically, this destruction presents in various stages of cell disintegration. The cells are pale and the nuclei stain very poorly. Frequently, in the most extensively damaged areas, all the structures are completely disintegrated. A sharp line of separation may be present between areas of necrosis and normal tissue, and, at these edges, considerable debris surrounded by a line of inflammatory cells is present. A curious feature of this pathology is the formation of cysts lined by inflammatory cells at the boundary line between diseased and normal tissue. These fluid collections increase in size due to the accumulation of pancreatic secretion. They are called pseudocysts to differentiate them from the true cysts of the pancreas which occur as a result of obstruction within the pancreatic duct without escape of the pancreatic juice. The walls of the true cyst are composed of pancreatic ductal cells (21).

The most severe hemorrhages in the pancreas are in the nature of true apoplexy. The gland may be changed into a large boggy hematoma which microscopically presents as a collection of erythrocytes and destroyed tissue. Since one may postulate tryptic digestion of the pancreas at the same time or even before the disintegration of the blood vessel wall occurs, necrosis of the pancreas is assumed to be a part of the picture. In only a few cases can the bleeding be traced to a disrupted wall of a medium sized pancreatic artery. Most cases are not of the apoplectic type. Necrosis and edema are of varying degree in different portions of the gland. Small collections of blood may travel into the tissues along the lines of the interlobular fissure and may even present underneath the peritoneum covering the organ. Microscopic evidence of necrosis is usually present and emphasizes the point that hemorrhage and necrosis invariably occur concomitantly.

There has been considerable discussion about the role of vascular lesions in the pathogenesis of pancreatitis. Under certain experimental conditions a vascular component is necessary for the laboratory production of pancreatitis. Popper and Neeheles (22) were able to incite pancreatitis in animals by occluding the superior

pancreatico-duodenal artery at the same time that the pancreatic duct was ligated and a pancreatic secretagogue was administered. Smyth (90) studied 40 cases of acute hemorrhagic pancreatitis and showed evidences of arterial thrombosis in 26 of these, or 65 %. Veins were more frequently thrombosed than arteries but it could not be determined whether these thrombi had formed before or after the inception of pancreatitis. Rich and Duff (20) demonstrated a vascular lesion in the veins and arteries of the pancreas, which lesion they thought led to rupture and hemorrhage. Necrosis of the media of the vessels was the outstanding feature. Rich and Duff ascribed this reaction in the vessel wall and the generalized reaction in the pancreas to the release of trypsinogen and to its activation into trypsin by contact with the hydrolyzed products of lipase digestion. Lipase acts upon the fatty tissue within the stroma of the pancreas and upon the extra-pancreatic fat with production of areas of fat necrosis which can be recognized as pearly white indurated structures. Since these hydrolyzed products include free fatty acids which cannot exist in the unconjugated state, there is immediate inactivation by combination with blood calcium. Large quantities of calcium may be mobilized from the blood in order to saponify the fatty acids (91). In some cases of pancreatitis, this may result in marked reduction in the blood calcium. Occasionally tetany becomes manifest (91).

Pancreatitis, thus, is at its inception essentially the result of the onslaught of the biochemical agents, the pancreatic enzymes. As the disease progresses without resolution, superimposed infection by various organisms, notably the colon bacilli and the staphylococci, produces suppuration and may result in pancreatic abscess.

Resolution may occur with fibrosis and calcification. Occasionally, with obstruction of a duct by fibrosis surrounding its wall or by a calculus within its lumen, a retention cyst may form (92). In some patients recurring attacks with varying degrees of fibrosis, necrosis and repeated fibrosis with calcification may lead to virtually complete destruction of the gland. The pathology of chronic pancreatitis is readily visualized in the light of this progressive process (93). A considerable portion of the gland is eventually replaced by fibrous tissue. Calcific areas are found throughout the gland and within the ducts. The mechanism of extraductal calcification is fairly well understood. Recently, Edmondson (85) has marshalled evidence to the effect that precipitation of calcium salts occurs within the lumen of an obstructed duct whenever the concentration of calcium rises above a critical level.

The effects of pancreatitis upon other structures and the body economy as a whole are of extreme interest. Death may occur within a few minutes of the onset of the disease. Many conjectures have been advanced to account for rapid exitus, death sometimes occurring within two or three days. Shock and its consequences undoubtedly play a role (94). Acute coronary insufficiency, as shown by electrocardiographic changes, accompanies the shock-like picture and may be the deciding factor (95). Certain important variations in electrolyte concentration, especially in calcium, sodium, and potassium may precede the demise (94). It is possible that adrenal cortical necrosis may also contribute to the collapse.

Diffuse peritonitis is a common accompaniment of acute pancreatitis, oc-

currence as a result of the collection of blood enzymes and the products of enzyme digestion within the abdomen and also as a result of superimposed infection. Diagnosis may be facilitated by paracentesis in the lower abdomen. A beefy, hemorrhagic fluid containing leukocytes, bacteria, and enzymes is typical of pancreatitis. A more localized type of peritonitis may follow in the lesser sac with the formation of a left subphrenic abscess. An adhesive peritonitis over the gall bladder, the colon, the stomach, and the under surface of the liver results in adhesions between these organs. Secondary ileus of the transverse colon and the upper jejunal loops, also, may result from the upper abdominal peritonitis.

Fundamentally, the pathology of pancreatic inflammatory disease can be deduced from the immediate and delayed effects of the pancreatic enzymes, trypsin and lipase, outside the pancreatic duct system (92). Much of the symptomatology, too, can be ascribed to excessive concentrations of these enzymes within the bloodstream (96, 97).

#### DIAGNOSIS

The diagnosis of pancreatic disease is, at all times, a challenging problem and has continued to plague the clinician. The old adage, "to think of it is to make the diagnosis," is not enough. Presumptive diagnosis of pancreatic disease are very frequently made, but remain, just as often, unproved or, what is worse, are accepted without adequate substantiation.

Our ability to detect signs of anatomical or functional abnormality of the pancreas is limited by the anatomic location of the gland, which makes it almost inaccessible to physical diagnosis, and by the large physiological reserve of the organ, which tends to obscure minimal metabolic defects. Indeed, extensive destruction of the gland may occur with a paucity of clinical signs (98, 99).

The clinical picture of inflammatory pancreatic disease, being of protean nature, offers little comfort in diagnosis; yet, the importance of an exhaustive history cannot be overemphasized (100). One of the most constant clinical features of pancreatitis, acute or chronic, is pain. Indeed, all patients suffering from prolonged severe upper abdominal pain, not otherwise explicable must be suspected of a pancreatic disorder (100). The location of the pain depends upon that portion of the organ which is diseased. Bliss et al. (101) have shown that pain arising from lesions in the head of the pancreas tends to localize in the epigastrium to the right of the mid-line; pain originating in the body of the pancreas tends to center in the mid-epigastrium; and pain due to disease of the pancreatic tail is concentrated in the left epigastrium. Pain from any part of the gland may be referred to the mid-back.

Among the important clinical associations in pancreatic disease are the sudden onset of mild diabetes (102) and the high incidence of pancreatic carcinoma in diabetes (103). Jaundice is seen when the inflammatory process of an acute or chronic pancreatitis involves the common bile duct or when carcinoma infiltrates the duct wall or metastasizes to nodes at the porta hepatis (104). Painless jaundice is a common observation in carcinoma of the pancreas. The

onset of jaundice without pain and accompanied by an enlarged gall bladder (Courvosier's Law) is sufficiently suggestive to warrant a diagnosis of carcinoma of the head of the pancreas. Recurrent jaundice has been in chronic recurrent pancreatitis and many cases of acute pancreatitis may evidence icterus at some time during the initial phase of the illness (105, 106).

When disease of the pancreas involves sufficient acinar tissue, defects in the formation of enzyme will cause fat and protein digestion to suffer (107). Thus steatorrhea and creatorrhea may result. Steatorrhea, however, must be considered a late sign of pancreatitis. Amongst 71 patients with proved chronic pancreatitis, Dreiling (32) encountered steatorrhea in only 9 patients (13%). Dornberger's (107) incidence was 50% and Maimon et al. (108) reported steatorrhea in 20% of his patients.

Study of the pancreas by X-ray is difficult because the organ cannot be visualized directly since it is similar in density to that of other structures within the abdomen. In addition, there is no known method of visualizing the pancreatic ductal system other than by reflux from the common duct during cholangiography and even under these conditions only about 20% of the cases will show the main duct (110). As yet, no radiopaque substance has been developed which, when injected into the bloodstream or taken orally will outline the pancreatic tract. The direct catheterization techniques of Leger (111) and Doubilet (112), while of great physiological interest, have limited diagnostic importance. Some lesions of the pancreas may be recognized by virtue of calcification within the gland, as in chronic pancreatitis with calcinosis, or in pancreatic cysts and pseudocysts in which calcification has occurred within the wall (113).

The roentgen signs of acute pancreatic inflammation (113, 114) are the presence of haziness in the flat film (115), obliteration of the psoas outline, elevation of the left diaphragm, pleural effusions (115), paralytic ileus and the so-called sentinel loop of the jejunum found in the left upper quadrant (116). If the patient's condition permits of barium ingestion, elevation of the stomach and widening of the distance between the stomach and the transverse colon may be demonstrated (109, 117).

Tumors and cysts of the pancreas (117) may be recognized, in many cases, by their pressure effects on surrounding hollow viscera which can be outlined by opaque media. Tumors in and about the region of the head of the pancreas, by pressure on the second portion of the duodenum, will cause enlargement of the curve and evidence of pressure on the medial aspect of the descending duodenum or on the greater curvature aspect of the pylorus or duodenal bulb (118). Mucosal distortion and narrowing of the lumen, displacement, and fixation of the loop may frequently be demonstrated (118). The Frostberg sign (the reversed figure-of-three of the duodenal loop) (119) has come to be recognized as a pathognomonic sign of carcinoma of the papilla or of the head of the pancreas.

The laboratory findings have assumed increased importance in the diagnosis of pancreatitis. Often, these represent the only means, short of exploration, whereby a diagnosis of pancreatic disease can be confirmed. Occasionally, blood sugar elevations occur in acute pancreatitis, indicative of temporary or even permanent



islet cell disturbance (102, 103); hyperglycemia is present in from 5–10 % of acute pancreatitis, but, for the most part, is of evanescent nature (103). Blood calcium depressions were first reported by Edmondson and Berne (91) and are due to mobilization of calcium from the blood into areas of fat necrosis. Values below 7 mg. % were usually associated with a fatal outcome. More recently, Edmondson et al. (94) have commented on lowered serum potassium concentration in cases of acute pancreatitis, levels below 4 meq./L. having been found in 19 of 27 cases. They have ascribed this hypokalemia to urinary loss, nasogastric suction, lowered potassium intake and to the alarm reaction with its alteration in adrenocortical function. These lowered potassium levels, in addition to the coronary insufficiency accompanying the changes in peripheral vascular dynamics, may be responsible for the electrocardiographic changes recorded by Gottesman, Casten, and Beller (95).

Precise early recognition of pancreatic disease depends upon quantitative tests of pancreatic function. These can be classified into three groups: 1. examination of the *Feces*, 2. examination of the *Blood Enzymes*, and 3. examination of the *Duodenal Secretion*.

The appearance of bulky, foul, greasy stools in pancreatic disease has been the basis of one of the earliest laboratory tests for disorders of the pancreas. In this type of test, the stool is analyzed chemically for nitrogen content, total fat, undigested fat, and fatty acid concentration. In order to obtain quantitative data, such an examination must be done after preparation of the patient for three days on a fixed fat diet (107). Stool analysis gives information not only as to the completeness of digestion but also as to the extent of absorption of foodstuffs. A high nitrogen, high total fat, high unhydrolyzed neutral fat, and low fatty acid content obviously mean incomplete enzymatic digestion. On the other hand, high nitrogen, high total fat, low neutral fat with high fatty acid content indicate incomplete absorption. From a theoretical point of view, these concepts are sound. In practice, however, there is an additional variable which affects both the completeness of digestion and the extent of absorption, i.e. the *intestinal transit time*. When the transit time is rapid, completeness of digestion and absorption is so interfered with that a positive differentiation between pancreatic disease and non-pancreatic disorders associated with hyperperistalsis or absorption defect is impossible. Thus, steatorrhea and azotorrhea may be seen in sprue, pellagra, Whipple's disease, hyperthyroidism, ileitis, ulcerative colitis, achylia gastrica and other intestinal diseases (32, 120, 121).

That patients with chronic pancreatitis display changes in stool composition is not to be doubted. The excellent studies of Dornberger (107) and others (122, 123) have shown this to be true. However, the observed changes are not specific and not diagnostic. In an unreported series of 71 patients with proved chronic pancreatitis, only eight had stool abnormalities (13 %). In Dornberger's series of 20 patients with chronic pancreatitis, there were six patients (30 %) whose stool analysis data fell outside the normal ranges. Amongst these 20 patients, there were ten mild cases and ten patients with advanced disease. These findings and the reports of others make it clear that stool abnormalities are evidenced only



in the advanced stages of pancreatic disease (120, 124). This latter fact, supported by the observations of Brunschwig (125) and other surgeons (126, 127) who have performed major pancreatic resections with surprisingly minimal digestive disturbances in their patients, has given rise to the impression amongst clinicians that the pancreas has tremendous reserve capacity. Unfortunately, this concept has been interpreted by some (128, 129) to mean that tremendous damage to the pancreas is required before there is an alteration of the pancreatic secretion. The concept of tremendous reserve digestive capacity is correct, and therefore analysis of the stool cannot be used as a quantitative test of pancreatic function. The concept of tremendous reserve secretory capacity is incorrect because the pancreatic function can be studied quantitatively by analysis of the duodenal drainage.

The most commonly used laboratory procedures employed in the diagnosis of pancreatic disease are the determinations of the blood enzymes. Serum amylase is the most easily measured enzyme. Its introduction in pancreatic diagnosis is the result of the classical investigations of Elman, Wohlgemuth, Somogyi and others have simplified the test and extended its usefulness (130-138).

Serum amylase is derived mainly from the pancreas and in small part from the liver and salivary glands (139, 140). It is almost always elevated at some stage in the course of acute pancreatitis, values above 200 Somogyi units (mg % glucose) being considered pathognomonic of the disease. The mechanism of the increase in circulating enzyme is assumed by Howard, Smith and Peters (141) to be backpressure within the pancreatic ductal system with retrograde passage of the enzyme through the capillaries into the bloodstream. Janowitz and Hollander (56) suggest that this increase is the result of an alteration in the exocrine-endocrine partition of the secreted enzyme.

Elevations of serum amylase to 8000 mg % or more have been reported in acute pancreatitis. In some of the milder forms of pancreatitis, a much smaller rise may be present for only a few hours, making it imperative for early and frequent examination in the course of the disease. Not infrequently a drop to normal may take place shortly after the onset of the disease, indicating early resolution. On the other hand, a sudden sharp drop may be indicative of extensive destruction of the pancreas with resultant lack of formation of the enzyme. In some clinics, the serum enzyme values have served as a measure of the severity of the process—lower figures interpreted as mild edematous pancreatitis and high values suggesting hemorrhagic and necrotic pancreatitis.

That elevations of the blood amylase are present early in the course of acute pancreatitis is a well established fact, though minimal elevations cannot be accepted as absolute proof of pancreatitis (142) nor does a normal blood amylase exclude pancreatitis. Increased blood amylase values have been reported in patients with perforated peptic ulcer, uremia, acute gall bladder disease, cholelithiasis, biliary dyskinesia, after cholangiography, and after morphine or codeine injection (143-152).

Serum lipase has been used by some to diagnose pancreatitis, especially in instances in which the blood amylase is normal (153-156). Unfortunately, lipase

determinations are not done in most laboratories because of the complexity of the procedure and the difficulty in defining the chemical and physical conditions of enzyme incubation. Urinary amylase levels have also been used by Dozzi (157) to diagnose pancreatitis in patients with normal blood amylase concentrations. Amylase is excreted from the blood by the kidney. Unless there is concomitant renal insufficiency the urinary amylase tends to parallel the blood levels (145, 158). However, the urinary amylase concentration under normal conditions is subject to great variations corresponding to fluctuations in the urinary specific gravity. The experience of most clinics with urinary amylase has not been encouraging (159).

While unanimity of opinion exists regarding the value of blood enzyme determinations in acute pancreatic disease, no such agreement attends the worth of these values in chronic pancreatic disease (160, 161). In chronic pancreatitis elevations of the blood amylase and lipase are assumed to be the result of obstruction to the flow of pancreatic juice through a ductal system which may be compressed by fibrotic tissue around it or by calculi within; in carcinoma of the pancreas cells may obtund the ducts. Johnson and Bockus (156) have reported hyperlipasemia in two-thirds of a series of patients with pancreatic carcinoma. Gambill, Waugh and Dockerty (162) have recently reviewed a case of pancreatic carcinoma in which both serum amylase and lipase were elevated persistently for a period of one year. They emphasize that this persistent elevation may be characteristic of pancreatic tumor. However, in most instances of chronic pancreatitis and pancreatic carcinoma, fasting blood enzyme levels have not contributed to the diagnosis (161).

The evanescence of amylase elevations in acute pancreatitis and the lack of significance of single determinations in chronic pancreatitis have led to the development of the provocative blood enzyme tests (147, 161, 163-175). In these procedures the level of the blood enzymes (amylase and/or lipase) is studied at intervals for several hours before and after the administration of drugs or combinations of drugs designed to: 1. stimulate the flow of pancreatic juice (secretin), 2. stimulate the production of pancreatic enzymes (doryl, mechoyl, urecholine), and/or 3. block the outflow tract of the pancreatic duct system (morphine, urecholine). These tests are based upon the physiologic concepts of Lagerlof (163) who administered secretin and morphine to patients, thereby inducing pancreatic flow in an obstructed system. He observed elevation in amylase amongst some patients and, occasionally in individuals with pancreatic disease, he recorded pain suggestive of biliary colic.

Depending upon the stimuli used, two types of responses have been described (171): 1. those in which the stimulus causes a rise in serum amylase in normal patients (the failure of amylase to rise is then indicative of pancreatic insufficiency as seen in chronic pancreatitis), and 2. those in which the stimulus causes no elevation of serum amylase in normal patients but does induce rises in those with pancreatic duct obstruction (a positive response, then, would indicate pancreatic cancer). Despite initial promising reports (163-165), this approach has not been successful in the hands of most investigators (161, 168, 171, 175).

In a series of 192 patients studied with combinations of secretin, mechohyl, urecholine, and morphine, the blood amylase responses were not observed to be correlated with the known state of pancreatic function as determined by operation and/or the secretin test (175).

Recently, there have been introduced tests based upon the effect that the hypertrypsinemia of pancreatic disease has on the blood coagulation mechanism (176-180). Innerfield and his associates have reported elevated antithrombin titres in patients with acute pancreatitis even after the blood amylase has returned to normal (96, 179). High titres were also reported in pancreatic cyst (180), pancreatic tumors (181) and in some cases of chronic pancreatitis (96); in cystic fibrosis of the pancreas (182) low antithrombin titres were occasionally seen. Shingleton, Anylan and Hart (178), working along lines similar to the Innerfield group, have developed the paritol blood coagulation test for pancreatic diagnosis. By this procedure, a change in blood coagulability could be induced by the administration of a pancreatic secretagogue to patients with chronic relapsing pancreatitis and pancreatic cancer. The contributions of Innerfield and Shingletons and their collaborators are interesting and provocative but much study remains to be done before the significance and reliability of their procedures are confirmed and established.

The secretin test of pancreatic function represents an application of the secretin mechanism of pancreatic secretion to pancreatic diagnosis. The first quantitative studies of duodenal drainage were performed by Agren and Lagerlof (183) using a secretin prepared by Hammarsten (184). Their classical studies have been confirmed by numerous subsequent reports (185-192). In the secretin test, duodenal intubation is performed on patients after a twelve hour fast. Then, 1.0 clinical units of secretin per kilogram body weight is administered intravenously and the duodenal drainage is collected at 20 minute intervals for 80 minutes. Based upon the study of duodenal volume, bicarbonate concentration, and enzyme secretion after secretin, two types of responses can be described: 1. one in which there tends to be a reduction of volume with maintenance of bicarbonate and enzyme secretion, and 2. one in which the volume secretion is sustained but the bicarbonate response is diminished. The quantitative deficiency is characteristic of pancreatic duct obstruction as seen in tumor (193); the qualitative deficiency is indicative of chronic inflammatory or fibrotic disease of the acinar tissue (32).

The alteration of the secretin response in pancreatic tumor depends upon the site and degree of pancreatic duct obstruction (193). The changes in chronic pancreatitis depend upon the extent of parenchymal destruction (32). In acute pancreatitis, volume, bicarbonate or enzyme data may be abnormal or the secretin test may be entirely normal (32). The tendency of the external pancreatic secretion to return rapidly to normal ranges after an attack of acute pancreatitis severely limits the value of the secretin test in the diagnosis of acute pancreatitis. Indeed, its only importance may be in the prognostic sense in that the persistence of abnormal pancreatic secretion after subsidence of clinical symptoms in acute pancreatitis is suggestive of permanent pancreatic injury.

The data of the pancreatic response to secretin, together with corollary information concerning the patency and function of the biliary tract (194-197), can be useful not only in the diagnosis of pancreatic disorders but also in the elucidation of various related syndrome groups such as obstructive jaundice, the post-cholecystectomy syndrome, the diarrheas, and the colitides (32, 198-200).

Duodenal drainage obtained in the secretin test can be subjected to cytologic study. Lemon and Byrnes (201), using improved methods of collection and microscopic study, have obtained a high percentage of smears positive for cancer cells in patients with pancreatic malignancies. Others have been impressed by the diagnostic possibilities of duodenal cytology (202, 203).

In some instances of suspected pancreatic disease, the last resort in diagnosis may be exploration. In this connection it must be stressed that palpation of the gland is notoriously unreliable (204). In a study conducted on postmortem material, Libman showed many years ago that there was poor correlation between the microscopic findings of the pancreatic tissue and the descriptive reports of trained pathologists. Even biopsy cannot be accepted with complete confidence (205). Doubilet has stated that surface biopsies may be normal due to regeneration of acinar tissue, whereas deep wedge excisions, which are dangerous procedures, are more likely to reveal inflammatory changes. Erroneous information is frequently obtained in patients with pancreatic cancer. A small tumor may be surrounded by a large area of chronic inflammation so that, unless the tissue removed fortuitously contains a fragment of the cancer, a false sense of security may be given by the pathological report (205).

*(To be continued)*



## FAMILIAL AUTONOMIC DYSFUNCTION\*

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A new syndrome in childhood, characterized by many manifestations of autonomic dysfunction, was described in 1949 by Riley, Day, Greeley, and Langford (1). By 1952 Riley (2) reported upon a total of 33 patients with this condition collected from several sources. The principle features of this syndrome which were almost constantly present in all cases included: defective lacrimation, skin blotching, excessive perspiration, drooling, emotional instability, motor incoordination, hyporeflexia, and relative indifference to pain. All the patients were of Jewish extraction and a review of the family histories of affected siblings indicated that the disease was probably transmitted as a recessive characteristic. Another group of features were not so persistently present in all patients but were frequently the major presenting complaints. This group included: hypertension, cyclic vomiting, frequent pulmonary infection or unexplained fever, breath-holding spells, urinary frequency, mental retardation, convulsions, and corneal ulcerations.

The present report is based upon our experience with 16 patients with this disease seen at The Mount Sinai Hospital, Bellevue Hospital and in private practice. A study of the case histories of these patients revealed that the cardinal symptoms and findings were similar to those noted by Riley. We were impressed by the frequency with which an early correct diagnosis was missed because the presenting features simulated other conditions of the pulmonary, circulatory, gastro-intestinal or central nervous systems. Although this syndrome is of primary interest to those concerned with the treatment of children, the presenting complaints of these patients are so varied that the neuropsychiatrist, gastroenterologist, ophthalmologist or other allied specialists may be consulted for diagnosis or treatment. The present report will emphasize the differential diagnostic aspects of the major symptoms in relation to the systems involved or to the presenting syndromes.

### NEONATAL SYNDROME

An analysis of the neonatal course of the 16 patients in this series indicates that in 14 cases there was a definite history of neonatal difficulty. One patient was asymptomatic until the middle of the first year; in the other case, no neonatal record was available.

Shortly after birth several of the infants developed apneic or cyanotic spells with hypothermia. Generalized weakness with poor cry, diminished spontaneous activity, excessive oral secretions and respiratory distress supervened so that cerebral birth injury, atelectasis or pneumonia were suspected diagnoses. High fever, at times, was associated with abnormal signs in the chest or in other instances occurred without obvious cause. Many of the patients presented diffi-

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culty in sucking and swallowing with regurgitation or vomiting so that gavage feeding or an indwelling polyethylene catheter were employed. Although many of these findings resembled those seen in premature infants, only two weighed less than 2500 Grams; these infants weighed 2200 and 2000 Grams and were not among those most severely involved.

The neonatal difficulty, rather than disappearing by the time the infants left the nursery, usually heralded further disturbances. Several of the infants continued to vomit repeatedly, some in projectile fashion, so that hypertrophic pyloric stenosis was suspected and the patients were treated with thickened feedings and atropine. Failure to do well in terms of weight gain, psychomotor development and vigor aroused considerable concern. Unexplained bouts of fever and pulmonary manifestations, to be described later, made their appearance. Persistent hypotonia and muscular weakness with severe impairment of sucking and swallowing were severe in 2 patients and suggested the diagnosis of amyotonia congenita.

#### PULMONARY MANIFESTATIONS

Repeated episodes of pneumonia or bronchitis were the prominent feature and the cause for frequent hospitalization of 7 patients in the present series. The episodes were characterized by fever, cough and dyspnea and usually were associated with diffuse signs in the chest. In all instances the pulmonary difficulties began during infancy and extensive investigations were carried out in 6 patients for a presumptive diagnosis of fibrocystic disease of the pancreas. In many of the patients the sudden appearance of moist rales in the chest at the time of feedings suggested aspiration; for this reason, lipiodol esophograms were performed in 5 patients for suspected tracheo-esophageal fistula. In four other patients pulmonary disease was not suspected clinically but was found on roentgenograms of the chest in the course of investigation for unexplained fever.

Roentgenograms of the chest varied during the course of repeated attacks and generally were characterized by varying combinations of infiltrations, emphysema and atelectasis. Lobar atelectasis has been found on occasion in 5 patients.

Nasopharyngeal and bronchoscopic cultures obtained during acute episodes have not generally yielded pathogenic organisms. Bronchoscopy was performed at least once in 6 patients and in most cases revealed only clear mucoid secretions.

#### GASTRO-INTESTINAL MANIFESTATIONS

The neonatal difficulty in sucking and swallowing has already been noted. While this persists in some of the infants, it gradually improves in most although there is generally a delay in the ability to take solid foods.

Severe recurrent attacks of vomiting were present in almost two-thirds of Riley's series (2) but were a cardinal feature in only four of our patients. The individual episodes may be precipitated by some emotional upset or minor infection, or they start without known cause. In most instances a dramatic personality change seemed to precede the onset of vomiting. The child became sullen and irritable with a schizoid-like withdrawal from the environment. Self-

destructive activity has been observed, such as tearing at the skin and eyelids and chewing on the buccal mucous membranes and the tongue. Severe vomiting persists without notable nausea and marked dehydration ensues. Parenteral fluid therapy has been necessary in most instances. The vomiting episodes continued for periods varying from one to four days and stopped without relation to therapy. Two patients in this series died during attacks of recurrent vomiting; in both instances the death was sudden and without correlation to the state of hydration.

#### CARDIOVASCULAR MANIFESTATIONS

Intermittent hypertension was found in 13 of 14 patients where blood pressures were recorded. Elevated blood pressures were most commonly found when the patients were subjected to stress of an anxiety provoking character. Associated with hypertensive bouts there were frequently marked erythematous blotching of the skin, hyperemia of the earlobes, cold hands and feet, and cyanosis of the fingers and toes. The blood pressure varied greatly from day to day and from hour to hour and was usually found to be normal during sleep. Diastolic pressures were usually strikingly elevated with a narrow pulse pressure. For example, in one patient during a one hour period the blood pressures varied from 124/110 to 184/160. Narrowing of the fundal arteries was noted in one patient.

The occurrence of symptoms strongly suggesting hypotensive attacks were described by the parents of many of the patients. These included "black-out spells", fainting and transient shock-like states. Riley has recently reported postural hypotension to be a common manifestation in patients that he has studied.

Some studies devised to ascertain the nature of the hypertension are to be reported elsewhere. The circulatory symptoms bear a marked resemblance to the "hypertensive diencephalic crises" in essential hypertension described by Schroeder (3) and by Page (4) with the exception that excessive lacrimation occurs during the episodes reported by these authors. Presumably neurogenic hypertension is mediated primarily through the autonomic nervous system with widespread vasoconstriction. The improvement noted during sleep and with sodium amytal are also indicative of the role played by neurogenic factors.

#### TEMPERATURE REGULATION

Striking fluctuations of the body temperature were present in nearly all cases. Although high fever was of particular concern to the parents and attending physicians, each child had periods of hypothermia ranging from 94-95°F for a day or two or for several hours if temperature charts were carefully observed. Hypothermia was of particular concern during the newborn period and several infants required long periods of incubator care despite a mature birth weight. Low temperatures were also noted during the early phase of cyclic vomiting.

Hyperpyrexia ranging to 105°F to 108°F was noted recurrently in most of the patients. During such attacks there was frequently little about the patient's appearance to suggest the height of the temperature elevation. At other times

the hyperpyrexia was associated with pulmonary manifestations so that a presumptive diagnosis of a pneumonia was made despite the failure to demonstrate pathogenic organisms in nasopharyngeal or bronchoscopic cultures. Fever was also occasionally associated with cyclic vomiting although it usually rose during the convalescent phase and after the patient was well hydrated.

Most patients had been treated with a great variety of chemotherapeutic agents and antibiotics without demonstrable effect, except when an obvious infection was present. Aspirin given in adequate doses was generally ineffective and varying degrees of sedation with phenobarbital or sodium amytal were also relatively ineffective.

#### CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Although many of the principle features of this syndrome are related to abnormalities in autonomic function, there are many indications of a more widespread involvement of the central nervous system.

The psychomotor development of the children we have studied has appeared to be retarded as judged by the usual standards based upon motor and verbal accomplishments. There is almost uniform delay in the age at which sitting, standing, and walking are achieved. The acquisition of speech is similarly delayed. Later psychometric examinations have shown considerable variation in the degree of retardation and did not always confirm the earlier impressions which leaned heavily on motor development.

Neuromuscular examination revealed that most voluntary muscular activity was performed in a poorly coordinated manner. The gait was clumsy, broad-based, stumbling, and at times ataxic. The speech was variously described as mumbling, dysarthric and indistinct. Muscle power and tone was generally reduced, at times markedly during infancy so that amyotonia congenita was considered. Deep tendon reflexes were generally absent, although active reflexes were present inconstantly in a few patients.

Decreased sensitivity to pain was frequently observed and was most strikingly illustrated by a 3 year old child who displayed a deformity of the wrist as the only evidence of a Colles fracture. During episodes of cyclic vomiting the patients commonly inflicted mutilating scratching wounds about the face, eyelids and the extremities without apparent pain.

Eight of the 16 patients had a history of grand mal seizures, although only 2 children had frequently recurrent spells. In the others convulsions were either infrequent or were associated only with hyperpyrexia. Electroencephalograms were performed in seven of the children and abnormal records were found in four without a specific type of abnormality.

Emotional instability dominated the behavior pattern of these children. An excessive anxiety was manifest toward any remotely threatening experience and only the slightest and most superficial adjustment was made to repeated exposure to the same stimulus, such as the routine physical examination. It was apparent that the anxiety was not related to pain inasmuch as there was little response to the actual painful stimulus, such as a hypodermic injection or a veni-

puncture, whereas the confrontation with a needle would result in a marked reaction of fear. The facial expression reflected this instability: a "silly" type of inappropriate grin frequently was present in the midst of unrelieved anxiety. Although these observations were made principally under hospital or clinic conditions, the parents were able to confirm similar behavior at home. The children appeared to prefer a stable environment with little variation in their daily behavior; any major change could precipitate a major crisis in the course of the disease.

The psychotic type of behavior which most frequently accompanied cyclic vomiting attacks has been described above. An acute manic reaction was observed in one patient who raced about the ward, tore off his clothes and resisted all restraint by scratching, biting and screaming. He was transferred to a psychiatric service where, after temporary improvement, there was a recurrence during which he suddenly vomited coffee-ground material, became apneic and died. No post-mortem examination was performed.

#### DISCUSSION AND SUMMARY

The principal features of 16 patients suffering from familial dysautonomia have been reviewed in an attempt to illustrate the varied presenting pictures exhibited by these children. The differential diagnostic features have been stressed since many other diseases of the gastrointestinal, central nervous, pulmonary, and cardiovascular systems have been suspected at times in these patients. The occurrence of these widespread evidences of autonomic and central nervous system dysfunction should arouse a diagnostic consideration of this syndrome, particularly in children of Jewish extraction. Since crying without tears is unusual after 3 months of age, this feature may supply a major clue to diagnosis, although many parents do not volunteer this information spontaneously and it is not commonly a cardinal presenting complaint.

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## MODERN DEVELOPMENTS IN CLINICAL CHEMISTRY\*

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The last 25 years have witnessed the evolution of laboratory equipment which permits the quick and serial determination of important blood constituents; its use eliminates cumbersome gravimetric procedures and, at the same time, operates in general on much smaller quantities of blood. The visual colorimeter, the photoelectric colorimeter, the spectrophotometer, and the flame photometer are milestones in this development.

In the following, some of the more recent ways and means will be exemplified by which blood constituents may be drawn into the orbit of photometric analysis. Examples for the clinical application of monomolecular layer techniques, of electrophoresis and of some methods of microbiological vitamin assay in the chemical laboratory will be given in the latter part of this article.

The great majority of chemical compounds are colorless and do not absorb lightwaves within the visible range. There are several ways to overcome this difficulty and to make compounds visible either to the eye or to the laboratory apparatus. We may extend the range of our vision into the infrared and into the ultraviolet regions of the spectrum. Particularly the latter has found wide application in biochemistry: characteristic ultraviolet absorption spectra are given by nucleic acids, by certain cyclic protein constituents, by bile acids, etc., but in general ultraviolet absorption techniques require relatively expensive equipment and have, therefore, not yet found the applications to Clinical Chemistry of which they are undoubtedly capable.

Another principle of introducing colorimetric methods consist in the conversion of colorless constituents into colored reaction products, either by actual changes, or by some form of staining with a dye. Both procedures are being used widely not only in clinical chemistry, but also in histochemistry which requires higher color intensities to achieve visibility under the microscope. Thus, the histochemist must set his sights higher than we in clinical chemistry, and a method that is satisfactory for histochemistry will usually be capable of easy translation into clinical colorimetry should one so desire. Many useful inspirations for new reagents and methods may be found in such books as *Histo- and Cytochemistry*, a compendium of histochemical methods by my former collaborator, D. Glick (1). Another source for useful color reactions is *Spot Tests* by F. Feigl (2).

The existing canon of clinical chemistry offers many well known examples for color reactions of the most common blood constituents. Some lesser known colorimetric determinations should be mentioned which have been used to good advantage in some special clinical studies; pyruvic acid in the study of certain liver functions may be colorimetrically evaluated as its pink 2,4-dinitrophenylhydrazone. The determination of lactic acid has presented great technical diffi-

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cultics, but may now be determined, e.g. as a load test for liver function, by its lavender color reaction with p-hydroxydiphenyl. Tartaric acid forms a beautiful amber colored complex with pentavalent vanadium (3).

The determination of enzymes by colorimetric methods has been greatly advanced by the introduction of highly colored substrates. Nitrophenyl phosphate is an excellent substrate for both the histochemical demonstration and the quantitative measurement of phosphatase activity (4). Phenolphthalein phosphate, while not commercially available, also holds promise for phosphatase determinations (5). In such instances the dye, being an indicator changing from colorless to yellow or red, is originally present in its colorless form and only when released by enzyme action can it be developed in its colored form through an appropriate change of pH.

A particularly sensitive group of colorimetric methods is based on the coupling of aromatic rings with various diazo-compounds. This type of reagent was particularly popular during the heyday of "sulfa" therapy. One of its less known applications is the determination of female sex hormones by their coupling through the aromatic ring A with Fast Black Salt K which we described several years ago (6). The reagent has been recommended by Heftmann (7) for developing chromatographic spots of estrone.

A novel idea has been introduced by Schwartzenbach (8), who takes advantage of the formation of chelates, cyclic complexes between polyvalent metal ions such as calcium, magnesium, iron and others with some colorless or colored complexing agents. As an example one may take the determination of calcium in 0.2 ml. of serum. Calcium forms a wine red complex with the dye Eriochrome black-T, a substance giving by itself a blue solution. When this is added in excess, a lavender colored solution results from the mixture of the red complex and the blue dye. This is titrated with the colorless, but powerful complex-former ethylenediaminetetraacetic acid (EDTA) and commercially known as Versene, which is 100,000 times more strongly bound to calcium and thus completely replaces Eriochrome black-T from the calcium complex. As soon as enough EDTA has been added to completely replace the Eriochrome black-T in the complex, the pure blue color of the Eriochrome appears. This method is widely used for the determination of the hardness of water. In the case of serum calcium a correction for magnesium is necessary, but since the amounts of the latter in the serum are fairly constant, a standard deduction for magnesium is satisfactory (9). We are using this method particularly for babies, when minimum amounts of blood only are available. Modified versions of this principle may be applied to other polyvalent metals when the need arises.

Blood constituents, which occur in quantities of an order of less than 1 mg. per 100 ml., usually will escape beyond the limits of sensitivity of the customary colorimetric procedures. At least in one such instance the chemical concept of catalysis has been adduced in an unexpected and elegant fashion; iodide ion catalyses the reaction between tetravalent cerium and trivalent arsenic which yields, by mutual reduction and oxidation, trivalent cerium and pentavalent arsenic. Of these four ionic species the oxidized cerium is the only one endowed

with color; the disappearance of this yellow ion with time is being observed colorimetrically. Its decrease runs strictly parallel to the quantity of the catalyst present, in our case iodine. This method is used in practice for the analysis of protein-bound iodine, the most useful procedure for the diagnosis of thyroid disease.

So far we have had a birdseye view of developments in analytical biochemistry, particularly in colorimetry. They concern modifications and improvements in the analysis of blood constituents of recognized clinical significance and thus belong to the actual practice of clinical chemistry. Some of them have yet to prove their value and significance for clinical practice; to this end the clinicians must be apprized of their existence, of their feasibility and their economy, which may bring them into the domain of clinical chemistry routine.

We shall now take a glimpse at some methods of the future which are still in an experimental stage: We have worked for a number of years on the properties of substances which can be spread out in extremely thin layers, actually one molecule thick, on aqueous surfaces. If one takes for instance stearic acid, one may spread it on a bath in a shallow tray. Simple computations and also certain optical measurements show that the stearic acid molecules are standing perpendicularly side by side like a crowd of people standing to watch a ball game. The molecules are 25 Angstrom long which is  $\frac{1}{10}$  millionth of an inch. By certain techniques these layers may be transferred on to metal or glass slides, the size of an ordinary microscope slide. We may expose such slides to various serum protein solutions and we find to our surprise that the stearic acid is taken up (desorbed) by serum albumin, but not by serum globulin. This phenomenon is highly specific for stearic acid and palmitic acid. Although, the amounts of stearic acid desorbed from the slides are minute, they can be measured very accurately by optical methods. We expect to correlate these data with pathological changes of serum albumin and its fractions.

Another application of monomolecular technique to clinical chemistry concerns the blood lipoids (10). One extracts the lipoids from a minute quantity of serum (0.2 ml.) with benzene and spreads it on a round glass dish about 20 cm. in diam. on water. On the same water surface is placed one drop of an oil which compresses the serum lipoid layer to a given area. The size of this area may be measured e.g. by tracing its outline on a sheet of transparent paper situated above. From the area in square cm. the amount and concentration of the lipoid in the serum can be calculated with a surprising degree of accuracy.

It would go beyond the scope of this paper to explain the principles of electrophoresis, a technique which permits the separation of closely related substances, primarily of high molecular weight such as the serum proteins, by placing their solution into an electric current. Depending on the electric charge of the molecules and their size and shape, they migrate at different rates. In the so-called "moving boundary" types of electrophoresis these fractions are visualized by the diversity of their refractive index, by stratification or with a German word "Schlieren" phenomena such as one may observe when e.g. water and alcohol are layered one above the other. By an ingenious mechanism the changes in refractive index

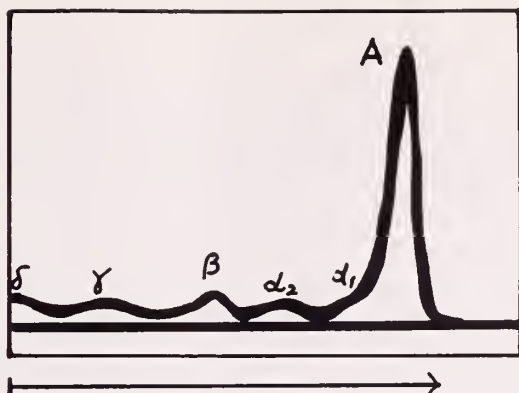


FIG. 1. Representative electrophoresis diagram of normal human serum. A, serum albumin;  $\alpha_1$ , alpha<sub>1</sub>-globulin;  $\alpha_2$ , alpha<sub>2</sub>-globulin;  $\beta$ , beta-globulin;  $\gamma$ , gamma-globulin.

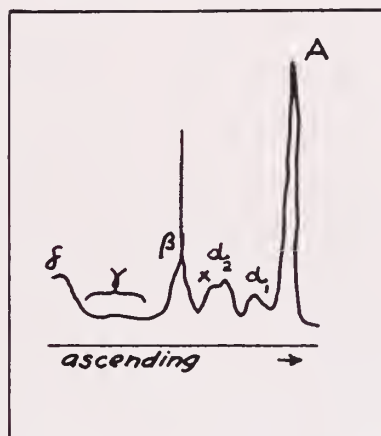


FIG. 2. Electrophoretic serum patterns in a case of hypo-gamma-globulinemia. For symbols see Fig. 1.

may be integrated and thus one obtains electrophoresis diagrams. Figure 1 illustrates the protein of a normal serum; it shows one big hump, the albumin and 4 smaller ones,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$  and gamma-globulin. Changes in these fractions permit us in a number of diseases to reach a diagnosis and to make a prognosis (11).

Figure 2 shows the serum of a girl in whom we had found a very high albumin globulin quotient before electrophoresis had been available. Subsequent checks by electrophoresis indicate that the patient completely lacks the gamma-globulin fraction which is known to contain most of the antibodies. This hypogamma-globulinemia, which was first observed in our laboratory about 15 years ago, has since been recognized in a number of cases. Surprisingly enough, the present patient has grown up and passed uneventfully through the usual number of children's diseases (12).

Severe globulin abnormalities have been observed in our laboratory and else-

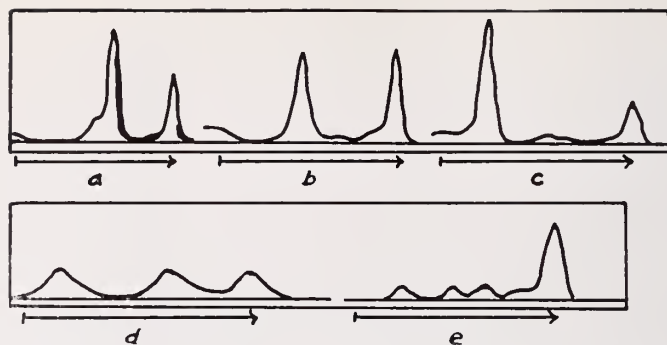


FIG. 3. Electrophoresis diagrams of serum of multiple myeloma patients. a, alpha-type; b, beta-type; c, gamma-type; d, multiple peaks; e, minor anomalies.

where in lupus erythematosus (13) and in Hodgkins' disease (14), in which for instance an increase in  $\alpha_1$ -globulin is of unfavorable prognostic significance.

Figure 3 comprises various electrophoresis diagrams in multiple myeloma; the serum in this disease shows a variety of abnormalities, the globulin fractions increase individually and accordingly one finds an  $\alpha$ -type,  $\beta$ -type, gamma-type, and multiple peaks-type (15).

While moving boundary electrophoresis requires expensive and intricate equipment, some of its tasks may also be performed by the much simpler technique of paper electrophoresis. Here, the protein solution does not migrate through a U-shaped glass tube, but a very small quantity of it is dropped on a strip of filter paper, at both ends of which a strong current is applied. After a number of hours, the strip is removed and dried and the protein may now be made visible by some indicator, such as bromophenol blue. This color may then be quantitatively evaluated by a densitometer and the findings registered, yielding a curve, which in general is identical with the graph obtained by moving boundary electrophoresis. Paper electrophoresis offers the additional advantage that a parallel paper strip can be stained for lipoids with such lipophilic dyes as Oil Red or Sudan Black. The increase of lipoids in the  $\beta$ -globulin fraction in nephrosis may be elegantly visualized by this technique, which also shows a stationary fraction of neutral fat at the point where the serum was originally placed.

While many vitamins occur in body fluids in sufficient quantity to make possible their determination by chemical reactions, there are a few, particularly cobalamine ( $B_{12}$ ) and folic acid, which run far below the limits of chemical detectability. These vitamins are determined by microbiological assay methods using bacteria and protozoa which have specific requirements for these vitamins; these assays are technically involved and full of pitfalls. In the course of work on the metabolism and nutrition of thermophilic microorganisms, bacilli which grow at temperatures up to  $80^\circ\text{C}$ ., we have developed methods and media that permit the rapid growth of such strains e.g. of *Bacillus stearothermophilus* and *B. coagulans* (16). These media are simple and inexpensive; besides they do not require sterilization, since the temperatures, at which they are used, prevent any contamination. Finally, because of their synthetic nature they are clear, so



that the amount of bacterial growth may be directly evaluated in a densitometer by their optical density.

In the case of  $B_{12}$  they have the additional advantage that the tests may be read in one or two days in contrast to the *Chrysomonas* and *Euglena* assays which require two or three weeks. We feel that these tests lend themselves particularly to introduction in small laboratories as they do not require complicated equipment but only thoroughly clean glassware and a 55° incubator. We expect to make these methods widely accessible by establishing a Vitamin Assay Station in our Department where we shall instruct interested parties in their performance.

Clinical Chemistry is a most dynamic scientific discipline which changes its aspects continuously. These changes are governed on the one hand by the changing demands and interests of the clinician and on the other hand by the onward march of analytical chemistry.

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# THE USE OF GAMMA GLOBULIN IN INFECTION REFRACTORY TO ANTIBIOTICS\*

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In 1945 Schick and Greenbaum (1) reported a case of edema and hypoproteinemia in a child who had almost no gamma globulin in her serum. When a similar case, published by McQuarrie (2), came to autopsy, a peculiar underdevelopment of the liver was found and it was assumed that a congenital defect in protein synthesis had existed.

The importance of gamma globulin in man as the carrier of antibodies is well established. This property of gamma globulin is particularly well demonstrated by its use as a preventive agent of certain viral diseases such as measles, viral hepatitis and poliomyelitis. It is well known also that antibodies carried by the globulin fraction may be effective against exotoxic and endotoxic bacterial diseases. This feature is exemplified by the use of immune serum in diphtheria and pertussis.

In 1952 Bruton (3) reported his observations of an eight year old child who suffered numerous viral and severe bacterial infections and showed evidence of deficient antibody production inasmuch as no gamma globulin was found on electrophoretic studies despite relatively normal levels of total serum protein. After that report a small number of cases with similar histories were seen by other authors. These patients failed to show gamma globulin on electrophoretic studies of their plasma though more accurate immuno-chemical analysis indicated the presence of minute quantities in some cases. With the exception of a normal response to vaccination with smallpox vaccine, there was no antibody response in these cases to artificial immunization with a variety of agents.

After the reports of agammaglobulinemia appeared, one of these investigators (4) discovered other patients who showed transient or partial deficiency of gamma globulin. Complete investigations of these patients' sera and their antibody production have not as yet been reported.

The discovery and use of antibiotics has brought about a revolution in the therapy of bacterial diseases; but, on the other hand, their effect against viral diseases, though perhaps not entirely negative, is still far from satisfactory. This fact is demonstrated in the cases of agammaglobulinemia in which attempts to prevent repeated infections by prophylactic administration of various antibiotics are only partially successful. However, when periodic injections of gamma globulin, obtained from pooled sera, are given to these patients, a striking protection is noted in each instance. The explanation of the benefit obtained would seem to lie in the fact that a congenital defect exists in reticulo-endothelial production of antibodies and synthesis of gamma globulin. The injection of the globulin temporarily provides the missing humoral antibodies.

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From the foregoing, it would appear that individuals, similar to those described, might be classified from the standpoint of their gamma globulin content as having an agammaglobulinemia which is either (a) permanent, (b) transient, or (c) partial.

In contrast to the rare instances of agammaglobulinemia, the practitioner encounters a number of cases where the infectious process does not respond at all, or in an unsatisfactory manner, to treatment with sulfonamides or antibiotics. Globulin studies, when done, do not indicate the patient to be suffering from any form of agammaglobulinemia. The physician may then be of the opinion that: 1. either the infectious agent is resistant or has become resistant to the antibiotic chosen, or 2. a new disease has been superimposed because fresh cultures may reveal different organisms, or 3. a virus is the etiologic agent. Nevertheless, when therapy is changed accordingly, and the results are still unsatisfactory, treatment seems to have reached a dead end and the question arises if there be a way out of this dilemma. Such patients might be classified into a second group—those with normal globulin content but who for some reason lack the specific antibody needed against the infection present.

As it has already been demonstrated that patients with permanent agammaglobulinemia can be benefited by the injection of gamma globulin obtained from pooled sera, it therefore would seem possible, by using this material, to reach a solution to the problem of refractory infection in individuals with normal globulin content but who probably lack a specifically needed antibody.

For this study we selected patients who had initially received adequate treatment for their infection, and in some, after subsequent cultures and alterations in therapy, had either not responded at all or only in an unsatisfactory manner. The cases include infections of the upper respiratory tract, lungs, or both, and the gastro-intestinal tract. None of the six patients responded satisfactorily to the therapy given in the hospital; four of them had been treated previously at home.

#### CASE HISTORIES

*Case No. 229778\**: L. V. a four month old white female infant was admitted on February 25, 1952. Two weeks before, she had developed a cough which had become progressively worse (but without spasmodic character or accompanying cyanosis) and a discharge from the right ear. By the end of the first week, after receiving penicillin and terramycin for four days, the aural discharge had cleared but the cough had persisted. A low grade temperature had been present during this period and was still 101.4°F at the end of the second week. Also at this time, fine moist inspiratory rales were heard diffusely throughout the chest. Because of the pulmonary findings and the persistent cough, hospitalization was advised.

Examination revealed an irritable and restless infant who weighed 4.9 kg. Some respiratory distress and mild cyanosis of the lips were noted. There was a mucoid nasal and post-nasal discharge, an acutely inflamed nasal and pharyngeal mucosa and an acute catarrhal inflammation of both ear drums. Diffuse moist

\* Patient of Dr. R. Norton.

crepitant rales were heard over both lung fields on inspiration. The rectal temperature was 99.4°F.

The hemoglobin was 70%; there were 3.73 M red blood cells and 7,900 white blood cells per cubic millimeter with 3% staff forms, 60% segmented neutrophils, 35% lymphocytes and 2% monocytes. Urinalysis was negative. Culture of the nasal discharge revealed a few colonies of *Staph. albus*; no growth was obtained from the throat. An x-ray of the chest revealed fine proliferative infiltrations in the left mid-pulmonic field and toward the base, diagnosed as bronchopneumonia.

Initial treatment consisted of chloromycetin and oxygen. During the following week improvement was satisfactory; the cyanosis disappeared, no respiratory difficulty was evident and the baby was out of the oxygen tent. The rales slowly diminished. During the second week, examinations revealed the naso-pharyngeal mucosa still inflamed and the pulmonary breath sounds were coarse. A slight cough had again developed and in the middle of the week inspiratory crepitant rales were again heard over both lung fields, particularly over the left upper lobe area. The temperature during this time ranged about 99°F rising once to 100.2°F. A second x-ray of the chest showed generalized prominence of the markings but no parenchymal infiltrations. A Vollmer patch test was negative. Nose and throat cultures revealed a few colonies of *Staph. albus*. Stool examination showed normal tryptic activity in diluted specimens and no starch or fat excess. Treatment was changed to aureomycin and by the end of the week the naso-pharyngitis had begun to disappear and no rales were heard over the lung fields. Through the third week, there was a recurrence of the respiratory difficulty with mild sternal retractions, cyanosis and coughing. An abundant muco-purulent nasal discharge developed and coarse rales were heard over both lung fields. The temperature ranged between 98.4°F and 99.8°F. Aureomycin was continued and penicillin was added to the treatment. Another chest x-ray showed proliferative infiltrations in the right and left lower lung fields, diagnosed as bronchopneumonia. At this time 20 cc of gamma globulin was given intramuscularly. Within 24 hours there was less respiratory distress and fewer rales were heard. One day later there was no respiratory difficulty and the nasal discharge had subsided. Another injection of gamma globulin (20 cc) was given; one day later the chest was clear of rales with only some roughened breath sounds heard. The infant was discharged five days later, general improvement having progressed satisfactory.

*Case No. 238775:* M. W. a premature white male infant was brought to the hospital on November 9, 1952 after being delivered at home. The infant's respirations were delayed in onset; he became deeply blue. When the respirations did commence, there was marked breathing difficulty.

Examination on admission revealed the infant to be deeply cyanotic, and the rectal temperature was 95°F. There were marked sternal retractions, crepitant rales were heard all over the chest and the breath sounds were diminished throughout the lung fields. The heart sounds were normal and a moderate tachycardia was present. The liver edge was palpable 3 cms. below the costal margin. The infant's birth weight was 1784 grams.

Nose and throat cultures revealed colonies of *B. friedlander*; a blood culture

was sterile. Urinalysis was negative. The hemoglobin was 115%; there were 5 M red blood cells and 12,200 white blood cells per cubic millimeter with 1% metamyelocytes, 3% staff forms, 67% segmented neutrophils, 30% lymphocytes and 28 nucleated red blood cells per 100 white cells. The blood type was O Rh positive; the mother's blood type was O Rh positive.

Treatment consisted of placing the infant in an incubator, supplying oxygen, using an aerosolized detergent for the atelectasis, and administration of penicillin and streptomycin. The umbilical cord required retaping; vitamin K (2.5 mgm) was injected. Improvement in the respiratory difficulty was rapid during the first 24 hours and slower thereafter. Aeration was normal by the fourth day and the oxygen was discontinued on the fifth day. Jaundice, which began to develop on the second day, became very deep during the following week. Despite polyethylene tube feedings of evaporated milk formula and supplementary clyses of saline and saline with glucose, the infant appeared very listless and weak. His weight at the beginning of the second week was 1639 grams. Examination revealed a few inspiratory crepitant rales over the left lung base. The liver was unchanged in position. A chest x-ray was negative. Cultures of the nose and throat revealed hemolytic *Staph. aureus* in addition to *B. friedlander* in the throat. Cultures of the blood and spinal fluid were sterile. *B. friedlander* was cultured from the urine and the stool. Urinalysis revealed a moderate number of fine granular casts and on another examination many coarse granular casts were seen, but only two to four white blood cells and one to three red blood cells per high power field were seen at any one time. A trace of albumin was found in each specimen. The hemoglobin was 114%, there were 5.3 M red blood cells and 16,900 white blood cells per cubic millimeter with 5% staff forms, 59% segmented neutrophils, 1% eosinophils, 28% lymphocytes and 7% monocytes.

Terramycin was substituted for the streptomycin in the therapy. By the middle of the second week of life, the jaundice had disappeared, a weight gain had occurred and his general vigor was much improved. During the third and fourth weeks of life, despite a continuous weight gain and excellent general condition, he began to have a daily temperature elevation at first to 101°F, later reaching 102°F. Examinations revealed only a mucoid nasal discharge and mild pharyngeal inflammation. Nose and throat cultures revealed hemolytic *Staph. aureus* (on one occasion a few colonies of *B. friedlander*). In the cultures of the urine (question of contamination) and stool *B. proteus* was found. The blood was sterile. Urinalysis continued to show coarse and fine granular casts, a trace of albumin and the same numbers of white and red blood cells as before. The hemoglobin was 71%, there were 14,000 white blood cells per cubic millimeter with 3% staff forms, 59% segmented neutrophils, 34% lymphocytes and 4% monocytes.

Aureomycin was used without effect on the temperature or the rhino-pharyngitis; gantrisin was added but without benefit. Toward the end of the fourth week, inspiratory distress developed. Fine crepitant rales were heard over both lung fields. The infant's general condition had rapidly deteriorated in spite of the antibiotics and the oxygen being given continuously. The aureomycin and



gantrisin were replaced by penicillin and streptomycin, however, the clinical condition continued to worsen and the respiratory distress was now present on inspiration and expiration. At one time respiration ceased, resuming after several minutes of artificial respiration and the administration of caffeine. Terramycin was added to the therapy. During the next few days the respiratory difficulty had subsided somewhat but the chest findings remained about the same. There was some further improvement through the week; however, during the sixth week there was sudden recrudescence of severe respiratory difficulty. A chest x-ray revealed proliferative infiltrations in both upper lobes. Nose and throat cultures revealed *Staph. aureus* and an occasional colony of *B. friedlander*. The total blood protein was 4.3 grams percent, with 3.2 grams percent albumin and 1 gram percent globulin.

At the end of the sixth week gamma globulin was given and repeated twice thereafter. The doses were 4 cc, 4 cc and 2 cc respectively. Within 24 hours of the first injection, respiratory distress had significantly diminished, and only slight labored breathing was noted after 48 hours. The temperature had dropped abruptly from 101°F, rose slightly and then slowly became normal. The chest became clear one week after the first injection, and resolution of the process was noted on chest x-ray taken at this time. His weight gain continued, there was no further temperature rise and he was discharged in the eighth week of life.

*Case of Newborn Female B:* The patient was born spontaneously from a frank breech position at term after an uncomplicated pregnancy.

At 24 hours of age, she was in acute respiratory distress. The cry was weak and moaning, there was flaring of the alae nasi, mild cyanosis and sternal retractions. A mild inflammation of the naso-pharyngeal mucosa was seen and fine inspiratory crepitant rales were heard over both lung fields. The temperature was 100.6°F. X-ray of the chest was reported as showing exaggerated markings. The hemoglobin was 124%, there were 7.9 M red blood cells and 9,300 white blood cells per cubic millimeter with 16% staff forms, 61% segmented neutrophils, 21% lymphocytes and 2% monocytes. A blood culture was sterile.

Therapy consisted of parenteral penicillin and streptomycin, and continuous oxygen. Twenty-four hours later when the condition was unimproved, terramycin was added and later continued with penicillin. By the end of 12 days of life, there had been little improvement in the general condition and none in the pulmonary findings. In addition there was now a muco-purulent nasal discharge. Nose and throat cultures revealed *Staph. aureus*; a blood culture was sterile. Throughout this period the temperature ranged between 98°F and 100°F. Antibiotic therapy was discontinued on the twelfth day of life; gamma globulin was given the next day and repeated two days later. The doses were 4 cc and 4 cc. The pulmonary findings began clearing within 24 hours of the first injection and no rales were audible after the second injection. The temperature diminished to normal after the second injection and the chest x-ray was negative. The infant was discharged well on the eighteenth day of life.

*Case No. 237111:* H. W. a nine and one-half month old white male infant was admitted with a history of illness of three weeks' duration. The illness began



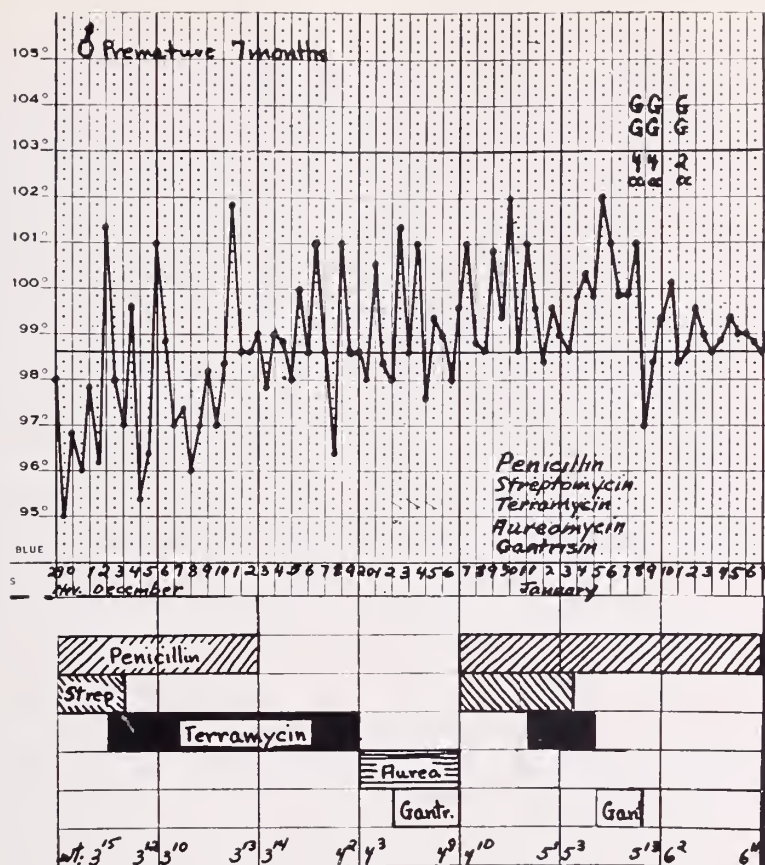


FIG. 1.

with the development of a loose cough, fretfulness and anorexia followed by frequent vomiting and diarrhea. The stools, which were brown and soft at first, soon became slimy, watery and green and as frequent as every half hour. Fever developed; the temperature rose sharply to 104°F. An upper respiratory infection was found when he was first examined at home. Treatment consisted of three penicillin injections, given every other day, terramycin, a cough mixture, a kaolin-pectate mixture and a restricted diet consisting initially of starvation and followed by boiled water and later diluted whole milk with Casec. During the first week the temperature oscillated between 102°F and 105°F becoming normal at the end of the week. The vomiting had stopped after the first 24 hours and the cough had lessened, but the stools were still frequent and loose. He was then hospitalized elsewhere but no additional physical findings were noted. Treatment consisted of starvation and the use of parenteral fluids and antibiotics (penicillin and streptomycin). After improvement, a diluted milk-Casec mixture was started. He was discharged at the end of a week improved, having been placed on a soft diet. During the week preceding this admission, the stools had slowly increased

in daily number and were becoming softer. The attending physician attempted to control this with a skim milk-Casee mixture and banana powder. However, by the day of admission, the watery diarrhea had recurred.

The infant's past history did not indicate any dietary intolerance. There had been one previous short episode of diarrhea at the age of seven months. Bilateral inguinal herniae had been present since birth but had never bothered the patient.

On examination he seemed irritable, and appeared pale and mildly dehydrated. He weighed 8.3 kg. The nasal mucosa was boggy and congested, the pharyngeal mucosa and tonsils were acutely inflamed and there was a thick green mucopurulent post-nasal discharge. The lungs were clear. The spleen tip and the liver edge were palpable just below the costal margin. A right indirect inguinal hernia was found. The cervical, axillary and inguinal lymph nodes were slightly enlarged. The rectal temperature was 99.2°F.

The hemoglobin was 81 %, there were 12,600 white blood cells per cubic millimeter with 3 % staff forms, 50 % segmented neutrophils, 43 % lymphocytes and 4 % monocytes. The carbon dioxide combining power was 46 volumes per cent. *Staph. aureus* in addition to diphtheroids and *Micro. catarrhalis* were cultured from the nose and throat. Trypsin activity was present in diluted stool specimens.

Treatment consisted of intravenous fluids and parenteral penicillin. Seven hours after admission, the right hernia had become swollen, very tender and irreducible. An herniorrhaphy was performed under ether anesthesia. Post-operatively there was some respiratory difficulty which was relieved by aspiration of mucus and the administration of oxygen for one day. Further laboratory work was done during the post-operative period: the total blood protein was 6.48 grams per cent, with 5.15 grams per cent albumin and 1.3 grams per cent globulin, the heterophile agglutination test was negative, a blood culture was sterile, and hemolytic *B. coli* and *B. proteus* were found on stool culture. The hemoglobin was 71 %, there were 3.4 M red blood cells and 12,200 white blood cells per cubic millimeter with 6 % staff forms, 62 % segmented neutrophils and 32 % lymphocytes. Urinalysis was negative. A Vollmer patch test and a chest x-ray were negative. A Widal reaction showed agglutination for Typhoid "O" in a dilution of 1:320 while that for Typhoid "H" was negative. Agglutination for Paratyphoid B was positive in 1:160 dilution and that for *Brucella* and *Proteus* OX19 were negative. Urine culture was negative and repeated stool cultures for *Salmonella* organisms during the next two weeks were negative. When the Widal reaction was repeated after two weeks, the agglutination for Typhoid "O" was positive in a 1:80 dilution, and for Typhoid "H" again negative. The agglutination for Paratyphoid B was positive in a dilution of 1:80. Specimens of the parents' stools did not reveal pathogenic organisms on culture.

Post-operatively the patient did well. His temperature ranged between 98.6°F and 101.4°F with daily elevations for 12 days. The wound healed satisfactorily and his stools became fewer and firmer. He was started on a powdered protein milk formula, tolerated this well, and was then changed to whole milk. However, during this period the inflammatory changes which had been seen in the upper respiratory tract had not changed significantly. Terramycin had been added to

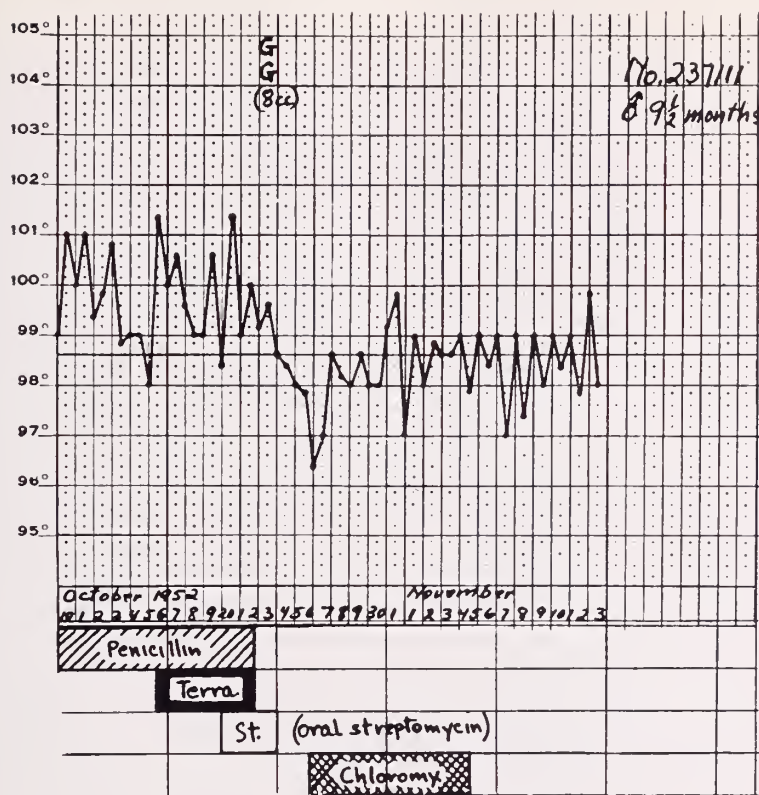


FIG. 2.

the penicillin without apparent benefit. It was decided to discontinue medication and give gamma globulin, the dose of which was 8 cc. During the next four days, the upper respiratory tract became clear and the nasal discharge disappeared. Because a pure culture of *B. friedlander* was found in the stool at this time, a course of chloromycetin was given when in vitro studies showed it to be sensitive to this antibiotic. There were no further symptoms at the end of this time and he was discharged well.

*Case 236943\**: I. G. a two year old white male patient was admitted early in October 1952 with a history since mid-August of repeated episodes of acute tonsillitis accompanied by fever. The temperature ranged up to 103°F and slowly declined with treatment, but usually remained normal only a few days before a recurrence of fresh symptoms. There were no other physical findings except for the inflamed tonsils and pharynx. Treatment consisted of the administration of either penicillin by injection or by mouth with and without aureomycin for a period of three or four days. There had been a two week period in September where there was no evidence of infection. Just prior to this admission, a fresh episode had occurred. After four days of treatment, the child began to complain

\* Patient of Dr. H. Rascoff.

of abdominal pain and developed loose stools, which soon became green, watery and were passed four to five times a day. He received sulfasuxidine, a kaolin-pectate preparation, and a restricted diet. The diarrhea had stopped for two days only to recur with a fever, the temperature reaching 103°F. In addition, tarry material was passed with each stool. With medication (penicillin and sulfasuxidine), there was no improvement and the temperature had remained about 103°F. Hospitalization was advised.

Examination revealed a pale child. The extremities were warm and there was no particular evidence of dehydration and the rectal temperature was 103°F. The ear drums were acutely inflamed, the naso-pharyngeal mucosa, tonsils and gums were acutely inflamed and there was a moderate postnasal mucoid discharge. The lungs were clear. The abdomen was soft and not distended, no masses were palpable and the bowel sounds were normally active. He weighed 12.6 kg.

The hemoglobin was 70 %, there were 13,600 white blood cells per cubic millimeter with 2 % staff forms, 74 % segmented neutrophils and 24 % lymphocytes. Urinalysis was negative. Staph. aureus and Micro. catarrhalis were cultured from the throat. No enteric pathogenic organisms were found on stool culture nor were any ova or parasites seen in stool specimens. An occult blood test on the stool was negative. Agglutination tests (Widal, Paratyphoid A and B, Shigella) were negative. The total blood protein was 5.97 grams percent, with 4.52 grams percent albumin and 1.45 grams percent globulin. Blood chloride, carbon dioxide combining power, and urea nitrogen were within normal limits. A chest x-ray showed proliferative infiltrations in the right mid-lung field toward the base, diagnosed as bronchopneumonia. The Vollmer patch test was negative.

Treatment consisted of penicillin, streptomycin and a soft diet. The febrile course persisted without evidence of clinical improvement during the first five days of hospitalization. A second blood count showed a 69 % hemoglobin, 3.68 M red blood cells and 18,000 white blood cells per cubic millimeter with 1 % myelocyte, 2 % metamyelocytes, 4 % staff forms, 67 % segmented neutrophils (with toxic granulation in each cell), 22 % lymphocytes and 4 % monocytes. Cultures from the nose revealed coagulase positive Staph. aureus, and from the throat Strep. viridans in pure culture. Both organisms were found later to be sensitive to terramycin.

When the temperature rose again on the fourth day, it was decided to try gamma globulin. A dose of 10 cc. was given. The temperature dropped sharply and reached normal within 12 hours, and then remained below 100°F. The upper respiratory infection receded within four days and the stools became firm and pasty. He remained in the hospital an additional period during which time a gastro-intestinal x-rays series was found negative. A stool examination done by the New York City Department of Health Laboratories showed Salmonella typhi murium.

*Case No. 236885\**: A.B. a two and one-fourth year old white female child was admitted October 2, 1952 for treatment of a persistent upper respiratory infection. The present illness began in the middle of September with a rhinitis which

\* Patient of Dr. H. Rascoff.



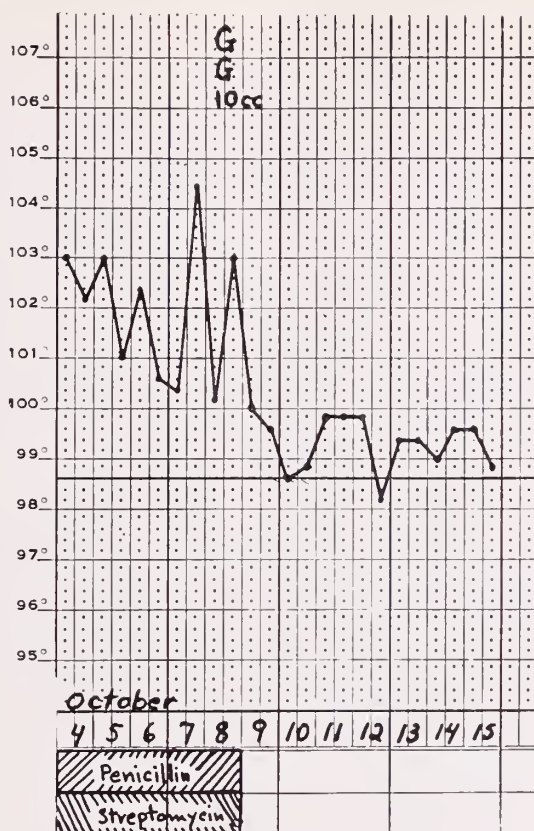


FIG. 3.

was treated with nose drops only. There was temporary improvement for one week with subsequent recurrence of the nasal discharge and the development of a fever (rectal temperature 102°F). Examination revealed an acute rhinopharyngitis and tonsillitis. Because of the frequency of similar infections in the past, it was decided to give penicillin in 6 daily injections supplemented by terramycin for four days. Diarrhea then developed but was readily controlled with dietary restriction and a kaolin-pectate preparation. During this six day period the temperature remained about 101–102°F rising once to 104°F. There was no clinical improvement in this time. Chloromycetin was then used instead of terramycin after which the temperature dropped to normal but without improvement of the other symptoms. Medication had been discontinued the day before admission; only aspirin was used when the temperature again rose to 104°F. Because of the persistence of the symptoms, hospitalization was advised.

The past history revealed that the child had an upper respiratory infection each month since early March 1952. Each episode was accompanied by a temperature up to 104°F, cough, running nose and diarrhea. Treatment had consisted of various antibiotics and sulfonamides given over a three to five day period and which apparently only temporarily controlled the infection.

Examination on admission revealed acute catarrhal otitis media on the left, rhino-pharyngitis with a mucoid nasal and postnasal discharge, gingivitis, glossitis and acute tonsillitis. There was slight general lymphadenopathy. The patient weighed 13.5 kg.

The rectal temperature was 99°F. The hemoglobin was 68 %, there were 3.58 M red blood cells and 13,500 white blood cells per cubic millimeter with 3 % staff forms, 59 % segmented neutrophils, 33 % lymphocytes and 5 % monocytes. Urinalysis showed a one plus acetone. Hemolytic *Staph. aureus* and *Micro. catarrhalis* were cultured from the nose and throat. No enteric pathogenic organisms were found in the stool culture. Urine culture was sterile. No ova or parasites were seen in stool specimens. A Heterophile agglutination test was negative; viral agglutination studies were negative; the Widal and other febrile agglutination tests (Paratyphoid A and B, *Brucella* and *Rickettsia*) were all negative. A Vollmer patch test and the chest x-ray were negative.

Treatment initially consisted of a soft diet and aspirin. The temperature began to rise on the fourth hospital day and reached 105°F on the fifth day. Penicillin and streptomycin had no particular effect on the course. Aspirin and intravenous fluids brought about only slight improvement—the temperature diminishing to 101°F and rising to 103°F. At this time 10 cc. of gamma globulin was given. Within 48 hours the temperature was normal, the nasal discharge and the upper respiratory infection had subsided. During the next three days the gingivitis and glossitis as well as the respiratory infection had almost completely cleared. The temperature remained normal. The patient was discharged two days later.

#### DISCUSSION

From the foregoing histories, it is evident that treatment presented a problem; the response to antibiotic therapy was obviously unsatisfactory and in three of the cases the general condition of the patient had become alarmingly bad. The bacteriological findings suggested an infectious process in five of the cases and, in four instances, this was supported by the occurrence of a leucocytosis with an increase in the segmented neutrophils. (See Table I for a laboratory summary.) It was possible that the use of antibiotics, especially where the illness was of some duration, resulted in either bacterial resistance, a changed flora and fresh disease superimposed on a weakened condition.

Some disturbance of the immune process must be considered as the cause of the patient's inability to combat infection. It has been pointed out that malignant diphtheria is the result of a dose of toxin fixed to the cells which is near or at the lethal level (5). Felton and Ottinger (6, 7, 8) when working with pneumococcus polysaccharide found in white mice a similar situation which they called an "immunological paralysis" because of the nature of the cellular union of antigen preventing antibody formation. Their theory implies that a patient so afflicted would demonstrate severe and even overwhelming disease because the specific antibodies were completely absent. Two of the cases, and possibly a third, in our series might be explained on this basis.

TABLE I  
Summary of laboratory examinations

CASE	CULTURES					DIFFERENTIAL WHITE BLOOD COUNT							BLOOD PROTEIN (grams per cent)		
	Nose	Throat	Blood	Urine	Stool	Total	Meta.	Staph.	Seg.	Eos.	Ly.	Mo.	Tot.	Alb.	Glob.
229778	St. albus St. albus	none St. albus				7,900		3	60		35	2			
238775	B. friedlander Hem. St. aureus Hem. St. aureus St. aureus	B. friedlander Hem. St. aureus B. friedlander Hem. St. aureus Few colonies of B. friedlander St. aureus Occasional colony B. friedlander	Sterile Sterile Sterile	B. friedlander ? contamination	B. friedlander B. proteus	12,200 16,900 14,000	1 3 3	67 59 59		1 28 34	30	7			
Newborn Female B	St. aureus	St. aureus	Sterile			9,300		16	61		21	2		4.32	3.32
237111	St. aureus	St. aureus	Sterile	Sterile	Hem. B. Coli B. proteus No pathogens B. Friedlander	12,600 12,200		3 6	50 62		43 32	4	6.48	5.15	1.3
236943	Hem. St. aureus	St. aureus Strep. viridans			No pathogens S. typhi murium	13,600 18,000		2 3	74 67		24 22	4	5.97	4.52	1.4
236885	Hem. St. aureus	Hem. St. aureus		Sterile	No pathogens	13,500		3	59		33	5			

TABLE II

*Quantities of pooled serum gamma globulin used in the cases described*

CASE	BODY WEIGHT, KILOGRAMS	QUANTITY		TOTAL AMOUNT
		per kg.	per pound	
229778	4.9	8.1 cc.	3.6 cc.	40 cc.
236885	13.5	0.74	0.3	10
236943	12.6	0.79	0.35	10
237111	8.3	0.9	0.4	8
238775	1.7	5.8	3.03	10
Newborn Female B	3.3	2.4	1.0	8

It is known also that in the course of a prolonged illness, a patient may become so debilitated that antibody production is depressed. The reticulo-endothelial system is incapable of developing good titers of antibodies. The function of the specific antibodies of the injected gamma globulin would be to combat the infection and to tide the patient over the stage of antibody depression.

The situation with viral diseases differs from bacterial infection in that the virus is an intracellular parasite which depends upon the utilization of enzyme systems for multiplication in the host cell. Practically complete invasion and damage of the cells has already occurred by the time symptoms become manifest. Therefore, viral infection would be less accessible to the beneficial effect of injected antibodies. In a patient suffering a prolonged illness with reemergence of symptoms of varying severity, the virus, which has continued its multiplication and has destroyed the affected cells, begins to spread to other cells. It is during periods of this swarming effect that the antibody content of the injected gamma globulin from pooled sera exerts its therapeutic value.

A large amount of the gamma globulin per kilogram of body weight was used in the first case, less was used in the subsequent patients, but when the dosage had been reduced to 0.6 cc to 0.8 cc per kilogram of body weight (0.27 cc to 0.36 cc per pound), the beneficial effect was still noted to be distinct (Table II). It was also seen that the same effect could be achieved with a single injection rather than multiple spaced injections.

During the course of this study 25 other patients with prolonged infections similar to those already described in detail received injections of gamma globulin. Despite the fact that the method of care and examination of these patients was not as extensively supervised, the clinical impression, nevertheless, was that distinct benefit had been obtained in well over half the cases. Because a beneficial effect was a rather consistent clinical impression, further studies of the "antibiotic" value of pooled serum gamma globulin are indicated. Such investigations are being continued and will be reported in the future.

## SUMMARY

This report describes a group of patients who had infections of the respiratory or gastrointestinal tracts, or both. Their response to treatment with antibiotics was unsatisfactory and they presented a problem as to further therapy.



Available information would appear to support the hypothesis that these patients possessed a normal amount of globulin but were probably deficient in the specific antibodies needed against the particular disease. Because of the large variety of antibodies carried by gamma globulin, especially when it is obtained from pooled sera, injection of this material offers a means of treatment of prolonged resistant infection.

An amount of gamma globulin from 0.6 cc to 0.8 cc per kilogram of body weight was found to be effective in curing the infections described.

#### ACKNOWLEDGMENT

The authors are grateful to Drs. S. Wasser, M. Goodman and H. Gall for their participation in this study. We wish to thank the Lederle Company, Pearl River, N. Y. for supplying in 1951 the gamma globulin with which this study was carried out.

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DR. RICHARD LEWISOHN

To Dr. Richard Lewisohn, Consulting Surgeon to The Mount Sinai Hospital, over many years a devoted and effective teacher and worker in the wards of the Hospital, important contributor to the development of gastric surgery, and independent discoverer of the citrate method of blood transfusion, "a signal contribution to the resources of medicine and to the welfare of humanity", the Alumni Association of The Mount Sinai Hospital takes great pleasure in conferring this Medal for Meritorious Service.



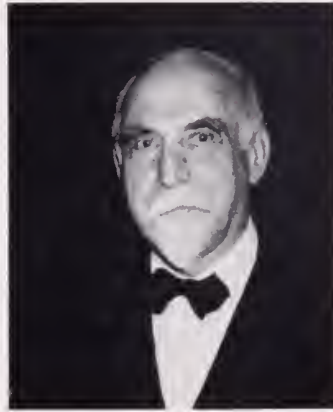
DR. BELA SCHICK

It is now 31 years since Dr. Bela Schick first came to The Mount Sinai Hospital and throughout that time those of us intimately associated with him have basked in his glory. Through his test for immunity to diphtheria he paved the way for active immunization against diphtheria. With Von Pirquet he coined the word and evolved the theory of allergy thereby explaining the etiology of nephritis. His role in the development of the tuberculin test and in the Nem system of nutrition remain outstanding contributions. Nevertheless, neither these nor many other original contributions surpass his accomplishments as a teacher, guide, and inspiration for younger and less experienced pediatricians. For all these accomplishments and because of its respect and affection, the Alumni Association of The Mount Sinai Hospital honors Dr. Schick and presents to him this Jacobi Medal. It is especially fitting that this medal, bearing the name of the founder of the first Chair of Pediatrics at The Mount Sinai Hospital, should be given to Bela Schick.



DR. DAVID BECK

To Dr. David Beck, physician, which proud title he has borne with dignity throughout his career, leader in community service, good friend and counsellor to all his colleagues young and old throughout a long and distinguished service to the Hospital, devoted worker for the alumni and its association, fighter for high ethical ideals, and staunch supporter of the good and right, the Alumni Association of The Mount Sinai Hospital takes great pleasure and pride in presenting this Medal for Meritorious Service.



DR. BERNARD S. OPPENHEIMER

To Dr. Bernard S. Oppenheimer, internationally known cardiologist, foremost among those to apply the electrocardiograph clinically in this country, bedside teacher and consultant in clinical medicine, pioneer contributor to the physiology, histology and pathology of the heart, co-discoverer of the cove plane or "coronary" T wave, pupil and associate of Sir Thomas Lewis under whose direction he shed new light on neuro-circulatory asthenia, untiring worker who continued his zeal for bedside medicine and clinical research into the years of his retirement, remarkable human being whose gentleness and love for his students, internes, and colleagues have earned him the highest esteem and genuine affection of all, the Alumni Association of The Mount Sinai Hospital takes great pleasure in conferring this Medal for Meritorious Service.

# *Important Notice*

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THE JOURNAL OF  
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# JOURNAL OF THE MOUNT SINAI HOSPITAL NEW YORK

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## CONTENTS

PROBLEMS IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS. <i>Selvan Davison, M.D.</i> .....	165
PANCREATITIS: A REVIEW (PART II). <i>David A. Dreiling, M.D. and Alexander Richman, M.D.</i> .....	176
SOME UNUSUAL CUTANEOUS, CARDIAC AND GASTROINTESTINAL MANIFESTATIONS OF SYSTEMATIZED AMYLOIDOSIS ASSOCIATED WITH MULTIPLE MYELOMA. <i>Joseph K. Perloff, M.D.</i> .....	195
MASCULINIZING TUMOR OF THE OVARY: SUCCESSFUL TREATMENT OF AN ARRHENO-BLASTOMA. <i>Gertrude Felshin, M.D. and Bernard Berglas, M.D.</i> .....	209
BENIGN TUMOR OF THE URETER. <i>Gordon D. Oppenheimer, M.D. and Lester Narins, M.D.</i> .....	213
STUDIES IN MYASTHENIA GRAVIS: CARDIAC AND ASSOCIATED PATHOLOGY. <i>Harvey Mendelow, M.D. and Gabriel Jenkins, M.D.</i>	218
ELECTRICAL RESPONSE OF THE CEREBRAL CORTEX TO CORTI- COPETAL IMPULSES: A COMPARISON OF PERIPHERAL AND CON- TRALATERAL CORTICAL STIMULATION. <i>Mortimer Ostow, M.D.</i>	226

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PROBLEMS IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS<sup>1</sup>

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Five years have elapsed since Hench and his associates published their signal discovery of the beneficial effects of cortisone in rheumatoid arthritis (1). Innumerable reports since have confirmed their findings and have established the value of cortisone in the management of rheumatoid arthritis. Established as well was the fact that cortisone was not a cure but only a palliative measure (2, 3). High suppressive doses have had to be sharply limited because of undesirable side effects (4, 5). As a consequence palliation in many cases is not too successful once the lower range of maintenance dosage is reached. The problem, then, of completely successful management of rheumatoid arthritis has not been solved. We have only added additional weapons, albeit powerful ones, to our armamentarium.

The following case reports present various aspects of the modern methods of treatment of rheumatoid arthritis. A general routine was established and is described now to avoid repetition with each case. Standard procedure included a high vitamin, nourishing diet; home methods of physiotherapy, e.g. heating pad, hot baths, strengthening and postural exercises, and correction of anemia. Patients receiving cortisone had their dietary salt restricted and were seen on an average of once every two weeks. A routine urine analysis was performed at each visit together with chest fluoroscopy and a physical examination. A semi-annual chest X-ray and electrocardiogram, and yearly gastrointestinal X-ray studies were carried out.

During chrysotherapy the routine included a complete blood count, urine analysis, physical examination and careful inquiries as to gold toxicity symptoms (pruritus, metallic taste, etc.) prior to each gold injection.

## CASE REPORTS

*Case #1.* P. T., 60 years old, male, was seen initially in September 1953, and had had arthritis for 22 years. There existed considerable deformity and limitation of motion of the hands, hips and knees. Rheumatic activity was present only in the left knee, which was quite warm, tender, much enlarged and very painful on motion. 80 cc of non-gelatinous, cloudy, yellowish fluid was removed from the left knee joint and 37.5 mg. of hydrocortisone instilled. The injection was repeated after a week. Marked improvement was prompt and he was quite comfortable for 6 months. In March 1954 the left knee was acutely inflamed again. The treatment was successfully repeated.

*Case #2.* L. G., 38 year old, male. Over a 12 year span rheumatoid arthritis was manifested by pain and development of severe flexion contractures and disability of both elbow joints, together with minor involvement of one knee and several phalangeal joints. He was treated variously with DOCA and vitamin C, intravenous typhoid vaccine, and chrysotherapy, all without success. In November 1950, cortisone therapy began, was beneficial,

<sup>1</sup> From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

and maintenance dosage was continued. This amount varied between 50-85 mg. orally, daily. In February 1953 intra-articular instillation of hydrocortisone into the elbow joints was initiated. On each occasion, 25-37.5 mg. were injected and repeated every 3-6 weeks as necessary. Coincidentally, the need for oral cortisone was diminished and 5 mg. were deleted every 2-3 weeks. By December 1953, systemic cortisone was no longer necessary and only the periodic elbow injections continued.

*Case #3.* A. Br., 70 years old, female. This patient had developed rheumatoid arthritis in December 1950 and rapid progressive flexion and extension deformity ensued in both knees. When seen in June 1952, she had been considerably improved by extensive physiotherapy, but a great deal of pain, tenderness, warmth, deformity and disability remained. She received intra-articular injections of 25-37.5 mg. of hydrocortisone into each knee. Remarkable improvement resulted, indicated by greater mobility and range of motion and exceedingly diminished pain, tenderness, swelling and warmth. These injections have had to be repeated every 3-6 weeks as dictated by returning pain.

*Comment* (Cases 1, 2 and 3). Intra-articular instillation of hydrocortisone is favored by little or no local reaction and by an absence of generalized side effects (6). Whenever possible, as in Case #1, the replacement of systemic corticosteroid therapy by intra-articular is desirable. Cases #2 and 3 exemplify situations where systemic cortisone was never necessary.

Only when one or two joints are significantly involved can we hope to approach the goal of not employing systemic corticosteroids. Remissions in a treated joint cannot always be expected to last for several weeks or more. Often, only a week's benefit is obtained. In such situations, adjuvant systemic therapy may have to be considered.

The amount of hydrocortisone needed differs in the various joints. Large sites, such as the shoulder, hip and knee, usually require 37.5 mg. at each injection. For the wrist and ankle 15-25 mg.; the tarsal joints 10-15 mg.; the metatarsal and metacarpo-phalangeal and the interphalangeal joints 5-10 mg.

*Case #4.* M. F., 62 years old, female. Rheumatoid arthritis began in 1947 and there have been recurrent episodes of relapse and remission. From July 1951, the arthritis was progressively worse and intravenous pontocaine and procaine, and physiotherapy were ineffective. Chrysotherapy was started but after 30 mg. microscopic hematuria appeared and gold was discontinued. Oral cortisone was instituted in March 1952 with immediate relief, and a maintenance dose of 75 mg. daily was established. Vague gastrointestinal symptoms developed after several months, but in November 1952 a roentgen examination was normal. These symptoms subsided and then recurred, and in March 1953 another gastrointestinal roentgen series revealed a prepyloric lesser curvature gastric ulcer. Following an adequate peptic ulcer regimen the abdominal symptoms disappeared. Since no emergency existed cortisone was withdrawn slowly. The arthritis quickly reappeared and to a marked extent. In May 1953, Xrays did not reveal the gastric lesion and an exploratory laparotomy was therefore not indicated. Reactivation of the ulcer had not occurred by April 1954 as indicated by negative roentgen examinations and continued quiescence of symptoms. Cortisone in the amount of 75 mg. daily was renewed in August 1953 and in October, 60 mg. of hydrocortisone was substituted. Increased arthritic symptoms appeared and subsided following reversion to cortisone. Recently, the two most severely affected joints, the right knee and the right wrist, have been injected with 37.5 and 10 mg. of hydrocortisone respectively. Maintenance dose of cortisone has subsequently been lowered to 55 mg.

During the entire period of steroid therapy, the blood pressure remained at pre-treatment levels, between 160/90 to 200/110. There was an occasional trace to one plus glycosuria.

Painful Dupuytren-like contractures developed in the flexor area of the right index finger. This has been injected successfully with 10 mg. of hydrocortisone.



*Comment.* This case features a number of problems. Hypertension was present when cortisone therapy was instituted. Despite two years of treatment there has been no evidence of cardiovascular complications. Unless otherwise indicated hypertension per se does not rule out the use of corticosteroids. Similarly, the recurrent glycosuria was never paralleled by overt diabetes mellitus. A serious situation arose as a result of the discovery of a gastric ulcer. The cortisone was gradually reduced so as not to produce severe withdrawal symptoms. On a strict medical regimen, the ulcer rapidly disappeared. Since the arthritis had become severely disabling, as a calculated risk cortisone was re-introduced.

Gastric ulcer has been described following corticosteroid therapy (7, 8). Theoretically its discovery contraindicates continuing such treatment. In this case, because of the alternative of a crippled, bed-ridden patient, the decision was to use cortisone, of course with constant clinical and X-ray supervision. After 14 months, the ulcer has not re-appeared. Via the introduction of intra-articular hydrocortisone, the amount of oral cortisone has been diminished. 55 mg. a day of cortisone by no means has produced anything like a complete remission. The important factor here as in all cases is that large maintenance doses produce serious side reactions, while no cortisone at all is catastrophic. A nice balance must be established, whereby despite the presence of active disease, a significant degree of liveability is acquired.

*Case #5.* R. W., age 59 years, female. This patient has had rheumatoid arthritis for 26 years and has multiple deformities. She began to receive cortisone in June 1950 and was seen at long intervals. Cortisone intake was somewhat irregular and averaged 75 mg. orally, daily. Early in 1951 she received 8 intravenous injections of post-partum plasma (9) without benefit. On May 14, 1951 she had been physically overactive, but had no respiratory or other infection. That night she complained of excruciating pain in her right knee, with unwonted heat, tenderness and disability. An acute arthritic flare-up was diagnosed and 25 mg. of hydrocortisone were instilled intra-articularly at her home. In retrospect the aspirated fluid was recalled to have been thick and discolored. When examined next day at the hospital, any movement of the right lower extremity was agonizing, and even at rest the pain was almost as severe. The rectal temperature was only 100°F and the white blood count normal. The knee joint was again entered and thick, purulent material was withdrawn. A direct smear revealed many pus cells but no bacteria. Cultures reported a pure growth of staphylococcus aureus A. Following sensitivity tests, she was treated with 2,000,000 units of penicillin and one gram of streptomycin intramuscularly daily. Cortisone was discontinued. The joint was aspirated every third day and 160,000 units of penicillin instilled. On two occasions streptokinase (50,000 units) and streptodornase (12,500 units) were introduced into the joint with the object of aiding liquifaction of the contents for easier withdrawal. A cast was not applied, only a firm elastic bandage. After six days there was distinct improvement. On June 15, aspiration resulted in a dry tap. Antibiotics were discontinued on June 19. Weight-bearing began on June 24, and the final result was a generally stable knee with not very much diminished mobility compared with the pre-infection status.

By June 9, the infection was considered to be safely controlled, and since the rheumatoid activity had become generally severe, re-introduction of cortisone was thought to be safe.

*Comment.* Acute pyarthrosis superimposed upon a rheumatoid joint has been described. In each instance, a primary focus of infection was noted. Such a focus was absent in this case and a search of the literature elicited no similar report. Whether the cortisone was in any way responsible for lowering the local cellular defenses against infection is problematical.



In any event, an infection that in pre-antibiotic days was certain to result in a useless joint, was successfully combatted by an intensive course of parenteral penicillin and streptomycin plus intra-articular penicillin and liquifying enzymes. The re-institution of cortisone may have aided resolution of inflammatory tissue and helped achieve earlier mobility (11).

*Case #6.* A. B., 61 years old, female. The onset of rheumatoid arthritis of large and small joints was in 1947, at which time a course of chrysotherapy was beneficial, as was a second course in 1949. In 1950 the arthritis became active and progressive. Intramuscular cortisone was begun and a favorable clinical course was pursued on a maintenance schedule of 100 mg. one to two times weekly. In January 1951 the patient fell and sustained fractures of the left hip and wrist. A hip nailing operation was done and cortisone discontinued. A course of chrysotherapy was initiated and oral cortisone was added in May 1951. After two weeks of suppressive dosage cortisone was reduced to 75 mg. daily. The gold injections were not beneficial and were discontinued. After 4 months, 50 mg. of cortisone daily was the average dose. In September 1951 she complained of severe upper back pain and tenderness over the tenth dorsal vertebra was discovered. An X-ray revealed fairly marked vertebral osteoporosis, but no collapse. Calcium and phosphorus blood values were normal. Cortisone was continued and gradually reduced to an average of 37.5 mg. daily. 25 mg. daily of methyl testosterone and one mg. diethylstilbesterol was prescribed. After two weeks the back pain subsided and in two months had disappeared. Testosterone and diethylstilbesterol were continued twice weekly for several months. From March to November 1952, there were occasional exacerbations of arthritis, the sedimentation rate ranged between normal and 48 mm. per hour, and the dose of cortisone alternated between 50 and 75 mg. daily. The patient was instructed to diminish cortisone dosage by 5 mg. every two weeks and after several months a satisfactory maintenance level of 60 mg. daily was established.

*Comment.* Lowering high daily quantities of cortisone by large cuts such as 25 mg., frequently and quickly precipitate an acute flare-up of rheumatoid activity. Maintenance of a useful degree of clinical remission is accomplished best by small graduated, widely-spaced reductions.

As in Case #7, (see below), back pain developed. However, X-rays did not reveal collapse of any vertebrae, and as described above cortisone was not withdrawn. In so doing, a risk was taken. Under careful observation, perhaps aided by the tissue building properties of testosterone and diethylstilbesterol (10), the pain disappeared. Ignoring back pain and continuing cortisone despite persistence of pain would have been unjustifiable in the light of the known tendency to osteoporosis due to hypercortisonism (12, 13).

*Case #7.* R. H., 55 years old, female. Rheumatoid arthritis developed 17 years ago spreading gradually to the hands, feet and knees. When initially seen in March 1951 she had been receiving irregular courses of gold for 8 years at a large hospital clinic. This therapy apparently was of little value, but she wished to continue. Her food intake was very bad, particularly regarding protein, and a severe hypochromic anemia and vitamin deficiency existed. The mental status was a combination of self-pity, hypochondriasis, impatience and alternating hyperemotionalism and depression, all leading to extremely poor cooperation in general measures such as diet and physiotherapy. After 6 months the patient was not seen again until March 1953. Gold injections had been discontinued and she had been taking oral cortisone for one year. During that period medical attendance was irregular, with very little regulation of dosage or investigation for possible undesirable side-effects. At this time she was receiving 75 mg. of cortisone daily and was complaining for 3 months of persistent

mid-back pain with radiation to the right flank. Tenderness was elicited between D 11 and L 1 and an X-ray revealed a compression fracture of the twelfth dorsal vertebra.

Cortisone was discontinued immediately. She was placed upon KCl, 3 grams, calcium gluconate 4 grams, methyl testosterone 10 mg., and premarin 1.25 mg. daily. Strict bed rest was ordered, upon a firm board, without a cast or brace. After 3 weeks the back pains disappeared and mobilization proceeded gradually.

It was learned from the family that while receiving cortisone therapy, the patient's complaints and disability were not discernibly less.

*Comment.* The development of severe osteoporosis and the collapse of vertebrae has been reported (12, 13), and is not unexpected in hypercortisonism and its Cushing-like syndrome. Onset of back pain in a rheumatoid arthritic patient receiving cortisone must not be blindly ascribed to the disease. Immediate X-ray is indicated, and if not available, cortisone should be discontinued. Discovery of a collapsed vertebra is an indication for prompt cessation of corticosteroid therapy. Androgenic and estrogenic hormones have been reported as valuable in osteoporosis and should be used (10). Although acute psychiatric problems did not ensue, the initial use of cortisone may have been interdicted in this highly emotional, unstable personality (14, 15).

*Case #8.* M. F., 59 years old, male. For many years this patient has had psoriasis, kept more or less under control by chrysarobin and sulfonamide ointments. He was also a mild diabetic, controlled by diet. A cataract operation was performed in May 1953. Almost immediately afterward there developed acute arthritis of both knees and of many joints of his left foot. A trial of colchicine was completely unsuccessful. Butazolidin was employed with little or no benefit. In July 1953 his erythrocyte sedimentation rate was 95 mm. per hour (Westergren) and the blood uric acid was 4.75 mg. per cent. An electrocardiogram revealed a left bundle branch block and he had an effort angina well controlled with vasodilators. Aspiration of a knee joint revealed a cloudy, non-gelatinous fluid with many polymorphonuclear cells and lymphocytes, and no bacteria. Hydrocortisone into each knee joint was very beneficial, but too many small joints were involved to allow for similar treatment of the foot. The severity of the foot pain incapacitated him, and he could not work. Therefore oral hydrocortisone was started and he was quickly free of pain. Gradual reduction of the suppressive dose was effected, but even on 30-40 mg. daily of hydrocortisone glycosuria was marked. However, this has been easily controlled by 30 units of NPH insulin. Incidentally, the psoriasis has improved.

*Comment.* Contraindications to corticosteroid therapy were diabetes mellitus and coronary artery disease. Co-existent was the patient's pressing need and demand to return to his job, thereby barring long range trials of gold or of general measures. Intra-articular hydrocortisone has been effective in holding down the maintenance oral dose, and there has been no sign of cardiovascular embarrassment. Careful diet and moderate quantities of insulin have kept the diabetes well in check.

A sudden postoperative acute arthritis in a male ordinarily points to gout. The repeatedly normal blood uric acid, the unremitting clinical course and lack of response to colchicine and butazolidin eventually established rheumatoid arthritis as the correct diagnosis.

*Case #9.* E. M., 54 years old, female. Rheumatoid arthritis began in 1948 and therapy with testosterone and estrogenic substances, DOCA and vitamin C, typhoid vaccine, preg-

nenalone, and physiotherapy were not beneficial. Intramuscular cortisone in 1950 was effective, was discontinued in February 1951, and the remission continued until September 1951 when parenteral cortisone was re-introduced. This was replaced by the tablet form in January 1952. Because of an irregular response to the oral form the patient was referred for evaluation in November 1952. It was quickly elicited that 50-100 mg. of cortisone were taken daily, but all in one dose! Proper maintenance guidance was given and improvement promptly appeared. The following year witnessed her needs fluctuate between 65-75 mg. daily. Intermittent intra-articular hydrocortisone injections were given into the knees and shoulders.

Weekly urinalysis revealed occasional mild glycosuria. Her blood pressure varied between 130/70 and 160/90. In October 1953, hoping to decrease the need for systemic cortisone, hydrocortisone tablets 60 mg. daily were substituted. On November 20 she suddenly complained of severe dyspnea. When examined, the neck veins were distended, the blood pressure was 170/100 and the pulse 100 per minute with regular sinus rhythm. An electrocardiogram and a chest X-ray were not remarkable. Between November 20 and November 30 hydrocortisone was gradually discontinued. Digitalization was initiated and continued with digoxin. Mercurhydrin was injected on several occasions with good diuretic effect. By early December, except for slight dyspnea, the circulatory status was greatly improved. The arthritic status was extremely severe and generalized, and butazolidin 100 mg. t.i.d. was started. After one week there was no improvement, ankle edema was severe, and the drug was withdrawn. The arthritis was now so severe that cortisone therapy was renewed followed by prompt relief. A maintenance dose of 60-70 mg. daily was established, with 10 grains of aspirin every 4 hours as needed, and intra-articular hydrocortisone as indicated. At this time, with 0.25 mg. daily of digoxin there is no evidence of congestive failure, either objectively or subjectively.

*Comment.* Congestive heart failure closely followed a change from cortisone to hydrocortisone. The possibility of greater sensitivity to hydrocortisone than to cortisone is possible. Following elimination of the corticosteroids, a disabling arthritis rapidly re-appeared. After due consideration, it was decided to return to cortisone. The patient's dire need to return to work and to care for her home dictated the decision. The economics of a situation cannot be totally disregarded.

Despite exposure to cortisone for several years, glycosuria has remained transient and as such need not be considered a contra-indication to the drug. Patients should be carefully instructed in dividing oral cortisone allowance and to avoid the error of one or two large doses. Since oral corticosteroids act and dissipate quickly, large single doses are of no significant value.

*Case #10.* A. W., 54 years old, female. Following a severe pneumonia in March 1953, a disabling, acute polyarthritis appeared in April 1953. A course of 500 mg. of gold (myochrisin) was not successful. In September 1953, cortisone was started. Suppressive doses produced marked improvement, but when a maintenance of 75 mg. daily was reached, pain and disability were marked and transient glycosuria appeared. Hydrocortisone was substituted and she then complained in addition of insomnia, which was somewhat alleviated by a combination of 20 mg. of hydrocortisone twice diurnally and 25 mg. cortisone at night. A low salt, 1600 C diabetic diet was prescribed as well as iron for the severe anemia. The latter drug was not tolerated due to gastric distress. Larger amounts of corticosteroids resulted in abdominal distention, ankle edema and 2 plus glycosuria. Three days of butazolidin, 100 mg. t.i.d. produced marked leg edema and no benefit. Hydrocortisone was instilled into several joints on various occasions with moderate relief lasting about one week in each instance.

*Comment.* This case must be listed as an inadequate response to corticosteroids, and is a therapeutic problem. Indeed, a trial of high dosage of 100–150 mg. cortisone daily with 6–12 tablets containing aspirin, phenacetin and codeine produced the remark that “even the best days were bad”. Iron and vitamin medication were taken irregularly or not at all, with the excuse of digestive incompatibility. Physiotherapy was refused as “too much trouble”. Chrysotherapy and butazolidin were not beneficial and the latter produced edema. The psychological status was one of dejection and little hope, and irregular office visits. Despite poor food intake, and a low salt regimen, there has been a steady increase in weight, probably water. Intra-articular hydrocortisone has been temporarily helpful. There exists in this patient a great fear of side-effects from all drugs and this to a certain degree may retard progress. Continuation of cortisone must be strongly questioned in the light of the psychogenic aspects (14, 15), yet there seems little doubt that denied any therapy, she would be doomed to rapid crippling.

Several weeks ago the patient was hospitalized. She received one unit of whole blood, intramuscular iron, intra-articular hydrocortisone, intensive “pep-talks”, and a complete rest. She is now taking 50 mg. of cortisone and 3 to 4 codeine, phenacetin and aspirin tablets daily and for the first time reports progress physically and mentally. An occasional short period of hospitalization may sometimes have a distinct salutary effect.

*Case #11.* C. S., 48 years old, female. Over 17 years rheumatoid arthritis gradually progressed so that most small and large joints were severely affected. Following acute left knee infection 6 years ago, a synovectomy was performed with a remarkably good result of a knee free of pain or disability. Not so the other joints. In October 1952 severe, active generalized arthritis was found, with a sedimentation rate of 85 mm. per hour (Westergren) and oral cortisone therapy was instituted. After 10 days of suppressive therapy improvement was marked and gradual decrease in the daily dose was initiated. By November 1952 the sedimentation rate was 16 mm. and 50 mg. was the daily quantity of cortisone. Save for occasional mild flare-ups, the patient has been very well and takes 40–50 mg. a day of cortisone.

*Comment.* This brief history has been presented to exhibit the striking benefit of cortisone in a long-standing severely incapacitated arthritic. And over 1½ years, no undesirable side effects have been noted. The remarkable beneficial effect of a synovectomy upon a severely deranged knee joint was also of interest.

*Case #12.* R. De F., 36 years old, female. At the onset of active, generalized rheumatoid arthritis in 1951 general measures such as physiotherapy, salicylates and the rest were failures. She then received chrysotherapy and after 85 mg. of myochrisine, definite improvement was observed. Because of menstrual irregularities gold was discontinued, and she was fairly comfortable for 7 months. The arthritis then became rapidly worse and gold was again employed. Shortly thereafter, the right knee was markedly swollen and painful. It was aspirated and 25 mg. of hydrocortisone instilled, followed by rapid improvement. After 335 mg. of gold, some general improvement was reported and gradually increased for 10 months (1435 mg.). Malaise, pain and stiffness then began to return and the patient could not cope with her household duties. As a consequence cortisone treatment was added with rapid amelioration of the arthritis. A maintenance dose of 75 mg. was established and then replaced by 60 mg. of hydrocortisone. By February 1943 the daily amount was 35 mg. in



divided doses of 15 mg., 10 mg. and 10 mg. She felt very well, but the sedimentation rate was 44 mm.

Since October 1953, the white blood count began to rise and by February 1954 was 20,600 per cu. mm. with a shift to the left. The hemoglobin, red blood count and platelets were normal. Gold injections were discontinued in January 1954. In May 1954 the white blood count was 7,700 cu. mm. with a mild shift to the left.

*Case #13.* H. C., age 34 years, female. Rheumatoid arthritis with multiple acute joint involvement began in early 1951. General treatment and such measures as intravenous pontocaine and procaine were not helpful. Chrysotherapy was advised and after 150 mg. of myochrisine improvement was noted, and reached its maximum at 500 mg. Most joints appeared normal, but one ankle and a wrist remained moderately painful and enlarged, though not at all incapacitating. When 800 mg. were reached a trace of albumin appeared in the urine, and persisted, and shortly became 1-2 plus. Gold injections were discontinued and oral cortisone substituted in January 1953. The remaining evidence of arthritis quickly disappeared as did the albuminuria. Following several months of maintenance at 60 mg. daily, the daily quantity was slowly decreased by 5 mg. every three weeks. By November 1953 all therapy was eliminated and at this juncture the patient was completely free of any evidence of arthritis.

*Case #14.* R. G., 37 years old, female. Progressive, active, multiple arthritis began in November 1951 and by February 1952 the patient was bed-ridden. She received a course of 8 weekly post-partum plasma injections, but the arthritis became worse and the sedimentation rate higher. Chrysotherapy was advised and after 100 mg. of myochrisine definite improvement could be seen, and steadily increased except for occasional short-lived flare-ups in a single joint. By September 1952, after 930 mg. of myochrisine the patient was playing golf. The sedimentation rate was 10 mm. and the heretofore persistent anemia was disappearing. After 1075 mg. injections were made every two weeks, and by 1225 mg. (December 1952) the interval was lengthened to three weeks and very soon to four weeks. The last injection was in September 1953, and at this writing the patient appears completely well (May 1954).

*Comment on Cases #12, 13, 14.* Despite the large ripple fashioned by cortisone upon the sea of rheumatic diseases, there are many who believe that chrysotherapy has its merits. In case #14, a complete remission obtained solely under gold treatment, and similar therapy produced a very satisfactory improvement in case #13. The advent of probable renal damage dictated cessation of chrysotherapy and replacement by cortisone. Temporary partial alleviation of the arthritis occurred in case #12, but relapse began and here cortisone was added. The plan was to employ both drugs thereby hoping to use small doses of cortisone. Gold was withdrawn when there seemed to be no alteration in the clinical course.

In a patient with an early, acute rheumatoid arthritis, where structural deformities have not been produced, a trial of chrysotherapy is indicated. The procedure has been to inject 10 mg. of myochrisine twice during the first week, then 15 mg. once, and 25 mg. twice on a weekly schedule. This is followed by 50 mg. weekly until 1000 mg. has been received. If striking improvement is seen, the injection intervals are widened every several months to 2, 3 and finally 4 weeks. If after another 6 months, the patient is completely well, treatment ceases. Too rapid curtailment of therapy frequently induces a relapse. When 1000 mg. of gold have been injected and no definite improvement has been noted, it is usually useless to continue.

At all times, careful observation for gold toxicity is imperative. Until 1000 mg. are received, weekly complete blood counts and urinalysis is the rule, and are then performed at each visit.

The hematological changes in case #12 may be ascribed to cortisone (16); or to an underlying infection. The former is by far the more likely cause.

#### DISCUSSION

The treatment of rheumatoid arthritis is frequently trying. It must be tailored to fit individual patients. However, one can establish certain broad lines of procedure and the preceding cases exemplify most of these.

When rheumatoid arthritis is mild and not very progressive, attention to general health, simple physiotherapy and adequate analgesic drugs usually suffices. In the presence of early, active, severe progressive disease, particularly in the younger patient, gold may be tried. Even in the older patient, salutary effects have been observed. The availability of BAL (British Anti-Lewisite) and of the corticosteroids have markedly diminished the grave consequences of gold toxicity, while not detracting from the necessity for constant vigilance toward early detection of side-effects.

In the event chrysotherapy is unsuccessful or is losing its effectiveness, corticosteroids are recommended. The chronic case of rheumatoid arthritis with deformities and ankylosis does not look to respond to gold injections. However, in just such a situation cortisone can be most rehabilitating. In the elderly, possessing other ailments, judicious employment of cortisone may make all the difference between activity and a vegetable existence.

A constant target is the lowest maintenance dose of cortisone compatible with reasonable comfort and ability to carry on daily activities, the degree differing with each patient's needs. Effective lowering of cortisone dosage must be done slowly. A reasonable system entails diminishing the dose by 5 mg. every 2-3 weeks. In this fashion withdrawal effects and explosive relapses are avoided.

When one or two joints are severely affected and others slightly or not at all, intra-articular hydrocortisone can be very effective. Repeating these injections at necessary intervals may allow much smaller systemic needs.

Analgesic drugs, mainly salicylates, should be pushed to the point of tolerance. Codeine in small amounts may be added when indicated. A high level of aspirin rather than cortisone is preferred.

No additive benefit has been noted in patients treated simultaneously with gold and cortisone. Hydrocortisone systemically had not been more effective than cortisone. Adrenal corticotrophic hormones (ACTH) have not been employed because of the expense and nuisance of frequent injections. The use of a gel obviates the need for daily aqueous injections; but in the event of overdose and reactions it cannot be withdrawn and controlled as can the oral corticosteroids.

Butazolidine has not been used routinely and will not be discussed here. Rehabilitation methods and orthopedic procedures cannot be discussed due to lack of space.

## SUMMARY

Fourteen cases of rheumatoid arthritis have been presented and the several aspects of management discussed. Ten patients received systemic corticosteroids at some time. One of these eventually was weaned from the systemic drug and maintained on intra-articular hydrocortisone. Two patients were successfully treated solely with intra-articular hydrocortisone. No patient had to discontinue cortisone permanently through untoward side-effects, although a number of such effects were reported.

Eight patients received chrysotherapy. Treatment was ineffective in four instances. Twice, signs of gold toxicity predicated cessation of treatment. In one instance improvement was distinct but insufficient for the patient's needs and cortisone was substituted with good effect. Chrysotherapy alone apparently established a complete remission in one patient.

## CONCLUSIONS

The treatment of rheumatoid arthritis is by no means a patented, safely wrapped-up procedure called cortisone. Some of the problems attendant to the management of this serious disease have been presented and discussed.

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## PANCREATITIS: A REVIEW (PART II)

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### CLINICAL PICTURE

There is no characteristic pattern in acute pancreatitis but experience has shown that there is a definite correlation between the severity of the process and the intensity of symptoms. Not infrequently the milder forms of the disease may begin and end with a few non-specific symptoms such as vague digestive distress, indefinite pains or nausea, and the diagnosis is established only because an alert observer suspected pancreatitis and proved it by blood enzyme study. On the other hand, the severe fulminating type may go on to exitus within a short time after onset, to be diagnosed only at the autopsy table.

The vast majority of cases will, however, present a picture which will lead to the diagnosis. Certain predisposing factors are easily elicited. Obese people who have indulged in a heavy repast or alcoholic debauch are frequently stricken, possibly the fact of hypersecretion of the pancreas being responsible for production of the disease. The role of alcohol in the causation of pancreatitis has been discussed; alcohol has been reported as a precipitating factor in from 13% to 25% of all cases. Although the frequent association of gall bladder disease with pancreatic inflammations has been commented upon, it does not seem repetitious to emphasize that all reported series of acute pancreatitis show an incidence of over 50% with gall bladder disease.

*Symptoms.* The outstanding symptom of pancreatitis is pain, beginning in the mid-epigastrium and radiating to the back, the right upper quadrant, or to the left flank. Right upper abdominal pain will usually suggest cholecystitis; pancreatitis will be diagnosed only if the blood amylase is drawn as a routine in such cases. Occasionally, pain may be present in the left upper quadrant and the left flank, especially in cases in which the tail of the pancreas is involved.

Nausea and vomiting are seen in the majority of the cases. Constipation is a common complaint, although diarrhea is seen in individuals in whom the irritative peritoneal reaction involves the pelvis. The abdomen may or may not be distended.

Shock is present in the more severe types of the disease and the drop of blood pressure is often accompanied by cyanosis and dyspnea, indicating coronary insufficiency and myocardial anoxia (206). In many cases, the shock, in addition to being secondary to the severe peritoneal and generalized tissue insult, is a result of severe blood loss following erosion of a vessel by enzymatic digestion. Jaundice (104) is seen in from 10-25% of patients and is presumed to be due to obstruction of the common bile duct in its intrapancreatic and intraduodenal portion by edema of the pancreas. It must not be forgotten that jaundice may be due to exacerbation of concomitant biliary tract disease. Paralytic ileus may be present early in the disease as a result of the severe peritonitis or may occur later, secondary to electrolytic imbalance. Localized paralytic ileus is a characteristic early sign (116). Fever is rarely of a marked degree, usually ranging in

the lower levels between 100°F and 102°F. Higher temperatures are usually indicative of progression of the process or of superimposed infection and suppuration. In the fatal cases, high fevers may appear pre-agonally.

The clinical picture of the patient with chronic pancreatitis is not so clearly defined (99). If one correlates symptoms with pathology, the most characteristic symptomatology is seen in patients with the most advanced type of disease in which the pancreas has been transformed into a poorly-functioning fibrotic mass. Diabetes mellitus, of rather severe degree, not too responsive to diet and insulin, may be a most distressing feature and will contribute to the extreme deterioration of the patient (102). Malnutrition, anemia, and avitaminosis are typical of advanced chronic pancreatitis. These may be present even without diabetes and are the result of loss of digestive ferments which is reflected in disturbed digestion and incomplete absorption.

The fibrosis and calcification of chronic pancreatitis results in the narrowing and obstruction of the ducts. In addition, afferent pain fibres may be involved in the inflammatory process. Severe, unremitting upper abdominal pain, so characteristic of chronic pancreatitis, is due to this involvement of nerve fibre and also to the ductal obstruction.

*Physical Signs.* The patient suffering from acute pancreatitis is acutely ill and exhibits anxiety, pain, and generalized distress. The more severe cases are in shock from the very beginning, and deepening of the shock is indicative of rapid progression. Early appearance of shock suggests massive bleeding. Later development presupposes delayed hemorrhage or absorption of toxins from the peritoneum. The shock symptoms have also been attributed to hypertrypsinemia (96).

The heart findings are usually of little diagnostic value and, except for variation in rate, are not significant. The lungs may show evidence of fluid, especially at the left base in cases of pancreatitis involving the tail of the organ (115). This is presumed to be due to the close contact of the tail with the left leaf of the diaphragm. Significant but not diagnostic physical signs are elicited over the abdomen. Voluntary guarding of the upper abdominal musculature is almost universal. Tenderness over the upper left rectus and in the right upper quadrant is also encountered very frequently. No mass is felt in the early case nor is evidence of intestinal obstruction seen. Distention and ileus occur late in the moderate case and early in the fulminating type. These findings are sufficient to alert the observer to the presence of an acute abdominal incident but are not sufficiently specific to permit accurate diagnosis.

Bliss et al. (101), from their experimental study of pain patterns produced by electrical stimulation of various parts of the pancreas, found that pain originating in the head of the pancreas localizes to the right of the mid-line from the xiphoid to just below the umbilicus. Pain starting in the body is referred to the midline and pain arising in the tail is felt to the left of the midline from the xiphoid to the groin. Radiation of pain to the back may occur from all parts of the pancreas. Herrera and Jones (207) have shown that pain evoked by experimental stimulation of the common bile duct and upper small bowel is the same

as the pain of pancreatitis. This finding is explained on the basis of a common afferent nerve supply in the greater splanchnic and lower thoracic sympathetic nerves.

As the disease progresses, there will be noted some increase in subjective complaints and in the overall clinical picture of the patient. Epigastric tenderness and rigidity are more prominent. Distention increases to the point at which absent peristalsis may be appreciated by the examiner and ileus is definite. Frequently, the increase in size of the abdomen is due to a collection of blood and tissue detritus within the peritoneal cavity and shifting dullness with a fluid wave may be present (115). The development of a collection or pseudocyst within the lesser sac can rarely be appreciated on physical examination and their presence will be suspected only on X-ray study. Rectal examination is uninformative in most cases, but, in those in which a pelvic collection is present, boggiess and even a mass will be felt.

Of interest are Cullen's (208) and Turner's (209) signs. These indicate hemorrhage within the retroperitoneal tissues with extravasation of blood to the flanks and anterior abdominal wall. These signs are not common but, when present, are of great diagnostic help. The hemorrhagic tendencies of acute pancreatitis are reflected also by bleeding in the form of hematemesis, bloody diarrhea and by thrombosis in the various arterial and venous channels.

In chronic pancreatitis, so well described by Comfort, Gambill and Baggenstoss (84, 210), the patient has been subjected to repeated attacks of acute pancreatitis of varying degrees of severity. It should be noted that this is not the rule for in the majority of patients with acute pancreatitis the inflammatory process subsides without further manifestation of permanent damage. However, a small percentage of patients do suffer from recurring attacks which are made evident by severe painful episodes associated with disturbances of acinar and/or insular function. These disturbances, such as diarrhea and glycosuria, may be transient and present only in the acute phases. During periods of remission there may be little sign of derangement even though the pathology of the gland is progressing. Subsequently when calcification and fibrosis have replaced a large part of the pancreas, diarrhea, creatorrhea and steatorrhea are present with and without diabetes.

The physical examination of these patients may reveal no abnormalities in the early phases of the disease. In the later stages malnutrition and asthenia are prominent in association with the emotional changes seen in patients suffering from any prolonged painful syndrome. Occasionally, when the head of the pancreas is considerably enlarged by a cyst or pseudocyst has developed, these masses may be felt. Enlargement of the liver may occur secondarily to the malnutrition or to the alcoholic ingestion. Alcoholism and drug addiction may be resorted to as an emotional flight from the realities of the disease. The gall bladder is rarely, if ever, felt in the course of the disease. In the most advanced cases in which the pancreas is the seat of extensive calcification, the organ may be felt as a hard triangular mass deep in the epigastrium. Occasionally, pyloric obstruction occurs and the stomach may be felt as a large dilated viscus.

## TREATMENT

The immediate problem in management of acute pancreatitis is that of conservative versus surgical treatment. Until recently, the reason for most laparotomies in acute pancreatitis was the inability to make a positive diagnosis. Drainage of the lesser sac or a diversionary operation on the biliary tract, viz. cholecystostomy or choledochostomy, was the procedure of choice with the idea of by-passing the common channel (211). Demel (212) has surveyed a large group of cases operated upon in the early stages and has reported a 52-78% mortality plus the even more enlightening observation that the course of the disease was uninterrupted by the operation. Machella (213) has analyzed a large series of 410 operated cases which showed a mortality of 35.1% and a series of 354 cases which were managed conservatively and exhibited a mortality of 19.7%. He concluded that regardless of what method of treatment employed, a minimum mortality of 10% could be expected.

Conservative treatment of acute pancreatitis is utilized in the early period in practically all cases in which the diagnosis is definitely established (214-216). Since it is impossible in most cases to predict which cases will have a mild course and which will go on to serious complication, the same energetic therapy should be applied to all cases of acute pancreatitis or acute exacerbation of chronic pancreatitis. The best treatment, needless to say, is applied with the closest of clinical and laboratory study so that changes in electrolytes or in blood elements may be combatted within a short period of their becoming manifest in the laboratory, even before clinical evidence appears. The medical therapy of acute pancreatitis attempts to combat all the aberrations produced by the disease and restore the diseased pancreas to complete function.

The major symptom requiring treatment is pain and for this many drugs and procedures have been advocated. Morphine sulfate and other opiates relieve pain by their central effect. However, their well known action of producing smooth muscle spasm, especially of the sphincter of Oddi (217), may enhance the anatomical basis for exacerbation of the inflammatory process at the very time when the patient is experiencing a short period of temporary symptomatic relief. Demerol exerts much less spasmogenic effect and 100 mg. doses given every 4 hours will give relief from pain with much less possibility of undesirable side action. Nitrites are of proved value in relaxation of spasm of the sphincter of Oddi and of the intestinal musculature. Nitroglycerine 0.6 mg. may be administered sublingually but its effect is only short-lived and its hypotensive action may be deleterious in patients acutely ill and suffering from shock and myocardial insufficiency.

Banthine has been reported to give considerable relief from pain (218). Analysis of its pharmacologic action reveals several reasons for this. First, there is its action on the sympathetic ganglia with blocking of the sympathetic pain afferent fibres and possibly motor efferent fibres (219). Second, its depressant effect on gastric secretion and gastric motility serves to minimize the amount of hydrochloric acid entering the duodenum, thereby lessening the stimula-



tion of pancreatic secretion and, so to speak, "splinting" the gland. Third, spasm of the sphincter of Oddi is diminished by the decreased flow of acid into the duodenum and by the vagal depressant action of the drug itself. The administration of 100 mg. given intravenously in a slow drip over a four hour period is well tolerated by most patients (220). Tetraethyl ammonium chloride (221) may also be of great analgesic value by blocking the sympathetic and parasympathetic impulses at the ganglia and by the same antisecretory and spasmolytic properties which banthine possesses. Hexamethonium chloride has been used with the same rationale with only questionable effect. Procaine hydrochloride, by intravenous injection, has been proved of value in the relief of pain for several hours after injection. This action is due to its local anaesthetic, analgesic, and antihistamine properties which are responsible for relaxation of spasm of smooth muscle. However, the drug may produce side reactions and severe respiratory difficulties are occasionally encountered.

Nerve block (222) and epidural block (223) have been of value in the treatment of those cases in which there is severe persistent pain. Paravertebral sympathetic block and splanchnic block have been used extensively by Gage (224) and Mallet-Guy (225). Relief of pain is due to interference with the visceral pain afferent fibres in the various sympathetic trunks and sympathetic fibres supplying the pancreas. In addition, pain may be lessened by the depression of secretion and the vascular changes occurring in the pancreas secondary to interference with its nerve supply. Fractional epidural block is not of as much value as nerve block. It has been used by Berk et al. (226) with only variable success. These observers advise its employment only in conjunction with all other measures and not as a substitute.

General supportive treatment of the patient, in addition to the relief of pain, requires strict attention to fluid, electrolyte, and blood requirements. The presence of shock indicates replacement by blood or plasma and solutions of sodium or potassium chloride in order to maintain blood volume, blood pressure and adequate renal blood flow. Glucose should be given with caution because of the possibility of aggravating a diabetic state induced by the disease and also because of its known stimulating effect on pancreatic secretion. When hyperglycemia and glycosuria are present, small doses of insulin may be required.

Hypocalcemia is not uncommonly seen and its presence augurs a bad prognosis. The mechanism of its production has already been discussed. Low values are found in the severest cases and replacement by 10-20 ml. of 10% calcium gluconate should be given intravenously every day. Hypokalemia is not uncommon, as shown by Edmondson (94), and is due to increased urinary loss, excessive tissue destruction, diminished intake, nasogastric suction and the alarm reaction. Approximately 50 meq. may be administered either intramuscularly or, with due caution, intravenously. Care must be taken not to overload the kidney whose function may be impaired. Frequent blood levels and electrocardiograms should be taken to avoid toxicity.

Depressants of pancreatic secretion are of great value. Nasogastric suction serves to remove hydrochloric acid from the stomach before its entry into the duode-

num, thereby preventing formation of endogenous secretin. The withholding of all food and fluids by mouth acts to further lessen the quantity of gastric secretion and thus indirectly splints the pancreas. Barbiturates, bantnine, tetraethylammonium chloride and atropine are of use in this connection. Radiotherapy (227, 228) has been used to diminish pancreatic secretion on the basis of clinical benefits in the disease and certain experimental observations, viz. the lessening of secretion in chronic fistula dogs after radiation and the shortening of illness in dogs subjected to the experimental production of pancreatitis followed by irradiation (229).

Penicillin, aureomycin, and terramycin (41) are of importance in combatting infection. Aureomycin and terramycin are concentrated in the bile and are effective against the usual organisms found in peritonitis. Soybean trypsin inhibitor has been used by Coffey (230) with success, but this measure is still untried by others and should not be given until more adequate studies have been reported. corticotropin has been administered by Saypol (231) with good result in one very sick patient. However, the possibility of stimulating gastric secretion and thus augmenting endogenous secretin must be considered.

For the hypoglycemia and glycosuria, insulin will be needed until such time as the process has resolved. In some cases, especially those which go on to chronic pancreatitis, replacement therapy may be necessary indefinitely.

The treatment of chronic pancreatitis is far from standardized. Medical therapy, which usually is unsatisfactory, includes a high caloric, high protein, low fat diet supplemented by vitamins. Carbohydrate restriction and insulin are necessary if diabetes is present. The total caloric intake is divided into several small meals to minimize secretin formation and thus pancreatic secretion. Alcohol and tobacco are interdicted: the former for its indirect effect on pancreatic secretion and its direct action on the duodenal mucosa and the latter for its effect on the autonomic ganglia supplying the pancreas. Tobacco is also a stimulant of acid secretion. Substitution therapy includes pancreatin (8-20 gm.) daily for steatorrhea. The efficacy of pancreatin in relief of pancreatic enzyme deficiency is often disappointing. In cases in which the gall bladder has been removed, measures should be instituted which will favor a periodic relaxation of the common bile duct and pancreatic sphincters and the peri-ampullary muscle, if present. The biliary flush regimen recently suggested by Best (232) may prove helpful. All these measures aim to maintain a normal pressure relationship within the biliary and pancreatic duct systems by periodic relaxation of the sphincters. They also tend to prevent stasis within the duct systems.

For the most distressing symptom of chronic pancreatitis, pain, a sedative antispasmodic mixture such as atropine, 0.6 mg., and phenobarbital, 15 mg. is administered before each meal. Nitroglycerine and sodium nitrite also may be tried. Narcotics should be avoided if at all possible because of the high incidence of drug addiction in these patients.

In some cases, despite conservative therapy, pain, weight loss and incapacity for work persist. These patients become chronic invalids, deteriorate both mentally and physically, and almost invariably become addicted to alcohol or nar-

cotics. Such individuals are, as a last resort, subjected to definitive surgery. Numerous procedures have been advocated; their great variety is an index of the different opinions of the pathologic physiology of the disease and also of the indifferent success which attends each type of approach.

Most authorities will agree that the first point of attack is eradication of the underlying biliary tract disease (214, 215). Cholecystectomy for real gall bladder disease will produce a remission in about one third of the cases (210). It would seem that the initial operation is the most rational time to explore the common duct and to determine once and for all whether there is any evidence of obstruction at the papilla by stone or by inflammatory stenosis (233). Some authorities have advised prolonged drainage of the biliary tract by long-armed T Tubes for periods as long as 12 months (234). Choledochostomy allows for repeated cholangiography and manometric-radiographic study of the biliary tract (215). When there is evidence of distal common duct obstruction, surgical therapy is directed towards relief of this obstruction. Gambill et al. (210) have found choledochoduodenostomy to be superior to prolonged T tube drainage in such instances. Bower (235, 236) has advocated choledochojejunostomy Roux-en-Y. This procedure completely diverts the biliary flow from the pancreatic duct system and bypasses pathology at the peri-ampullary region. It has the advantage of minimizing retrograde regurgitation of intestinal contents into the biliary tree and, therefore, is said to exhibit a lower incidence of recurrent cholangitis, cholangiolitis, and subsequently biliary cirrhosis than does choledochoduodenostomy (237).

The more direct approach to functional and organic obstruction in the peri-ampullary region has been operations upon the sphincter of Oddi. The original endocholechoal operations of Colp and Doubilet (238), while feasible, has been abandoned because of occasional failure to interrupt the sphincter and because of fatal complicating hemorrhage attending the procedure. Transduodenal sphincterotomy has proved more effective and safer. Doubilet and Mulholland (45, 64, 112) have extensively reported their successes with sphincterotomy in the treatment of chronic pancreatitis and other pancreatic affections. Good results have also been reported by Jones and Smith (239) with sphincteroplasty operation and by Gillette (240) who advocates an external sphincterotomy.

Since pain is such a dominant feature of chronic pancreatitis, it is not surprising that attempts have been made by the neurosurgeon to treat this disease by interrupting the peripheral pain pathways. Nerve surgery, in addition, may lessen pancreatic secretion and, in this way, contribute to the relief of symptoms. Nevertheless, it is questionable whether autonomic nerve surgery affects the progression of the disease and accomplishes anything more than palliation (241-246). In fact, Ripstein (247) was unable to demonstrate any effect of sympathectomy on the course of experimental pancreatitis. Stripping of the cholechoal nerves from the common duct has been advocated by some (245, 246). Fontaine (247) and Mallet-Guy (249, 250) have employed splanchnic section for the relief of pancreatic pain. Smithwick (251), DeTakats (242), Ray (244) and Grimson (252) have reported good results with sympathectomy either unilateral or bilateral and with or without associated splanchnicectomy.

Vagotomy may prove of value in the treatment of chronic pancreatitis. Besides its antispasmodic action on the sphincter, vagotomy offers relief of pain by interruption of some afferent nerve pathways, by indirect diminution of pancreatic secretion through its action on the stomach (13) and, perhaps, by direct suppression of enzyme secretion of the pancreas (14, 15). Rienhoff (253) combined vagotomy with thoracolumbar sympathectomy; Cattell (254) has used it in conjunction with gastroenterostomy; and Richman and Colp (52) have added vagotomy to their diversionary procedure of gastric resection. Ripstein and Shaffarziak (255) reported a beneficial action of vagisection in experimental pancreatitis and in a clinical study (256).

Gastrointestinal diversion in pancreatic disease may be necessitated by mechanical obstruction of the duodenum. This may be caused by extensive fibrosis or encroachment upon the duodenum by a large cyst in the head of the pancreas. Gastroenterostomy may be used for relief of this obstruction. Recently, Richman and Colp (257), noticing the beneficial effect on chronic pancreatitis which followed subtotal gastrectomy for gastric ulcer, introduced this operation as a definitive treatment for the disease itself. They reported the effect of this procedure upon the course of the disease in three patients to be encouraging. The rationale for this operation has been discussed as a "splinting" of the pancreas. Cattell and Warren (254) have observed several patients who were not relieved by gastrectomy and reserve gastrointestinal diversion for those patients in whom disease of the stomach or duodenum warrants such an approach.

The direct surgical attack on the diseased pancreas includes procedures which are designed to relieve complications of the inflammatory process, procedures which attempt to eliminate etiological factors responsible for repeated exacerbation, and procedures which aim to remove the diseased tissue itself. Pancreatic abscesses and accumulations in the lesser sac and left subphrenic space obviously require incision and drainage. Pancreatic cysts are treated only when, by virtue of their size and situation, symptoms are produced by encroachment on other organs. It is surprising how often large cysts will suddenly disappear without operation. The ideal procedure would be extirpation by excision. This is not always feasible, especially in cysts of the head, and, if feasible, not always desirable because of the extent of surgery necessary for extirpation, viz. radical duodenopancreatectomy. Evacuation and external marsupialization of pancreatic cysts have been abandoned because of the high incidence of recurrence and because of the nuisance and deleterious effects of an external pancreatic fistula (258). Internal drainage may be accomplished by simple anastomosis of the cyst to the stomach (259), the duodenum (260), or to the jejunum (260) or, by what appears to be the procedure of choice, by Roux-en-Y cysto-jejunostomy (261). This procedure obviates the loss of vital pancreatic juice, electrolytes and the annoyance of a draining sinus. The hazard of regurgitation of intestinal contents into the cyst cavity is also minimized (262).

A number of procedures have been suggested and tried to overcome obstruction in the pancreatic duct system proper. Pancreaticolithotomy, though rarely feasible, has been accomplished in a number of reported cases (263). This may be supplemented by ligation of the main pancreatic duct as performed by Rien-



hoff (263) (to destroy the secreting pancreatic parenchyma) or by transection of the duct with reanastomosis to the duodenum or jejunum as suggested by Wangenstein and successfully accomplished by Cattell (264) (to prevent recurrence of pancreatic duct obstruction). These operations are technically difficult. As yet, they have not received adequate trial to permit estimation of their efficacy.

Pancreatic resection is performed as a final resort to eradicate the diseased organ in those individuals in whom incapacitating symptoms persist despite all other measures. This form of therapy is most applicable to those cases in which the disease process is most severe or limited to the left half of the pancreas. Distal pancreatectomy does not present an insurmountable technical problem. However, it is doubtful whether this procedure would benefit the majority of patients whose disease is diffuse and, if anything, most severe in the head of the pancreas (254). Total pancreatectomy has been performed for pancreatic calcinosis by Clagett (127), Whipple (265), Rhoads (215) and others. However, the high mortality of this operation coupled with the consequent diabetes and the probable severe metabolic disturbances (266, 267) render this form of treatment of doubtful advantage to the patient.

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# SOME UNUSUAL CUTANEOUS, CARDIAC AND GASTROINTESTINAL MANIFESTATIONS OF SYSTEMATIZED AMYLOIDOSIS ASSOCIATED WITH MULTIPLE MYELOMA<sup>1</sup>

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One hundred and six years ago Henry Bence-Jones found "a new substance occurring in the urine of a patient with 'mollities ossium' " (1). Several years later amyloid was given its name by Rudolph Virchow who found that it gave a reaction to iodine and sulphuric acid similar to that given by starch. Twenty years after that observation Adams and Dowse (2), publishing as Bence Jones did in a London journal, described the post mortem examination of a patient whose bones were "studded over with small irregular cavities," whose liver and kidneys were the seats of a "lardaceous change," and in whose marrow a "pinkish putty-like material" (3) was deposited. Since these first observations the association of amyloidosis with multiple myeloma has been abundantly confirmed, and though the nature of this association has been speculated upon (4-8), the reason for the selection of certain tissues as manifest sites of amyloid deposition remains obscure. There does, however, appear to be a peculiar affinity for connective tissue, especially the matrix of smooth and striated muscle (blood vessels, heart, gastrointestinal tract, skin, tongue and peripheral voluntary muscle). Since the symptomatology of amyloidosis largely reflects the functional impairment of the organs so selected, it is hoped that a descriptive analysis of some unusual expressions of this complication of myelomatosis will assist in the clinical interpretation of the disease.

The autopsies were performed and studied in the Department of Pathology of The Mount Sinai Hospital. The tissues were fixed in ten percent formalin. Specimens of bone and bone marrow were fixed in Zenker's solution. The slides were stained routinely with hematoxylin and eosin. Congo red, iodine green and methyl violet were used as special stains for amyloid.

## CASE I

The patient, R. S., was a 54 year old white housewife admitted to the Medical Service of The Mount Sinai Hospital with symptoms of angina pectoris and congestive cardiac failure. She had been in good health until about two years prior to admission when she noted the onset of aching pain in the shoulders, neck, and jaws with occasional low back pain radiating down the posterior aspects of the thighs. Approximately seven months later the initial episodes of progressive exertional angina and exertional dyspnea began, followed shortly by the gradual appearance of orthopnea and occasional attacks of paroxysmal nocturnal dyspnea. Six months prior to admission diurnal ankle edema of increasing severity

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began. A private physician administered several injections of mercurhydrin which produced diuresis and temporary symptomatic relief. At that time an anemia was discovered and treated with vitamin B<sub>12</sub>, liver and oral iron.

For the few months before admission the patient described increasing thirst accompanied by polyuria, frequency and nocturia.

During the year prior to hospitalization there had been anorexia, frequent bouts of nausea, occasional emesis, increasing constipation and a 50 pound weight loss. During this same period the patient suffered a marked loss of body hair beginning rather abruptly and sparing only the eyebrows and the scalp at the vertex of the skull. There were no other skin manifestations until three months prior to admission when she developed an erythematous, papular, intensely pruritic eruption beginning on the dorsum of the hands, then involving the trunk and face and finally becoming generalized.

Physical examination revealed an obese chronically ill, orthopneic, afebrile woman whose blood pressure was 140/70. The skin and mucous membranes were pale. There was virtual alopecia totalis sparing only the eyebrows and cranial vertex. On the face, trunk and extremities there was a patchy pruritic skin eruption consisting of macular and papular erythematous areas with evidence of extensive excoriation. The skin generally was somewhat thickened and inelastic especially over the scalp. The neck veins were full. There were bilateral crepitant basilar rales up to the angles of the scapulae. The heart was enlarged 3 centimeters beyond the mid-clavicular line in the sixth intercostal space. The rate and rhythm were normal. No murmurs were heard. A firm moderately tender liver edge was palpated three finger breadths below the right costal margin. A blunt, non-tender spleen was felt three finger breadths below the left costal margin. There was two plus pitting edema of the legs and ankles. Examination of the osseous system was unrevealing.

*Laboratory.* Hgb. 7 gms, WBC 10,000 with a normal differential. ESR 140 mm/hr. Sternal marrow revealed 50% myeloma cells. Urine: Specific gravity fixed at 1.010, albumin 4 plus, HCl ring and Jacobson test for Bence-Jones protein were both positive. The urinary sediment was loaded with white blood cells and clumps of white blood cells. Albumin/Globulin ratio 2.5/6.6. Positive formol-gel reaction. Test for cryoglobulins was negative. Stool guaiac—negative. Calcium 10.8 mg%, phosphorus 4.2 mg%, alkaline phosphatase 9 King-Armstrong Units. Blood urea nitrogen 45–74 mg%, creatinine 3 mg%, uric acid 12 mg%. Phenolsulfonphthalein excretion 20% in two hours. CO<sub>2</sub> content 54 vol.%, Chlorides 106, Sodium 134, Potassium 5 mEq/l. Bromosulphalein retention 26% after 45 minutes. Bilirubin 0.5 mg%, Prothrombin Time 15 seconds with control 13.5 seconds. Cholesterol 260 mg%. The electrocardiogram revealed ST segment depressions and T wave inversions as seen in myocardial involvement or after the administration of digitalis. The venous pressure was 24 cm with rise to 26 upon right upper quadrant pressure. The arm to tongue circulation time with decholin was 20 seconds. X-ray of the chest revealed increased transverse diameter of the heart. Complete skeletal survey disclosed generalized demineralization but no lytic lesions.

*Course.* The patient remained virtually afebrile. She was treated with digitalis, mercurhydrin, salt restriction and transfusions but continued to have occasional bouts of nocturnal dyspnea, slight but persistent ankle edema and mild attacks of angina pectoris. It was postulated that the heart disease might be due to cardiac amyloidosis associated with multiple myeloma. A diagnostic biopsy of the gingiva revealed deposits of amyloid in both vessel walls and stroma. An attached fragment of bone showed areas of hematopoiesis with masses of myeloma cells.

It was further postulated that the rash, the inelasticity, the thickening of the skin and the alopecia might be due to cutaneous amyloidosis. Biopsy from the right forearm was unrewarding but a scalp biopsy revealed amyloid in the stroma around hair follicles and sebaceous glands.

The patient's course continued to reflect moderate congestive heart failure and azotemia with the blood urea nitrogen fluctuating from 45 on admission to 26 and finally to 70 mg %. Acidosis was never present, and the blood pressure remained normal. There was persistent nausea and occasional emesis. The patient continued to complain of aching in the shoulders, neck and jaws. At the end of the fourth hospital week she suddenly became disoriented, hyperpyrexia, comatose and died shortly thereafter.

#### *Gross Autopsy Findings*

The body was that of a well developed moderately obese white female weighing 142 pounds. The skin was smooth with small dry, excoriated macular lesions scattered over the shoulders, arms and breasts. The body hair was sparse except for the eyebrows and a few grey hairs over the vertex of the scalp. There was no axillary or pubic hair. The *heart* weighed 360 grams. It was soft and flabby in consistency and presented evidence of dilatation of all four chambers with moderate hypertrophy of the ventricles. There was no gross evidence of necrosis or scarring. The coronary arteries were patent throughout with relatively few flexible yellow subendothelial plaques none of which compromised the lumina. The right auricular endocardium overlying the foramen ovale exhibited a fine greyish-brown translucent granularity. A thickened left auricular endocardium altered the flexibility of the chamber wall, the inner surface of which was diffusely white with similar greyish-brown punctate translucent granulations. *Lungs* together weighed 1420 grams. They were rather firm in consistency and moderately edematous. The pulmonary artery and its major branches were unremarkable but when the lung was sectioned the small vessels on the cut surface were rigid and gave the impression of fine granularity when the tissue was palpated. *Spleen* weighed 625 grams and was soft in consistency. On section thick, greyish-red material readily scraped from the diffuent surface and the small artery stood out remarkably everywhere. The *liver* weighed 1650 grams and was moderately congested. *Pancreas*—The small arteries presenting on the sectioned surface were firm and prominent. *Genito-Urinary System*—The right kidney weighed 140 grams, the left 184 grams. The cortices were granular and moderately atrophic. *Gastro-Intestinal System*—The esophagus was grossly normal

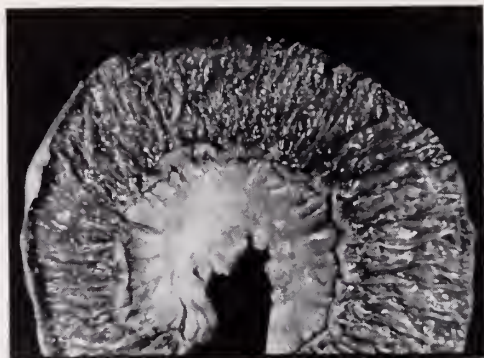


FIG. 1. (15339) Small Intestine showing prominent folds due to amyloid infiltration of the wall.

but in the stomach, the branches of the gastric arteries were firm and unusually prominent as they distributed themselves throughout the wall of the viscus. The network was even more striking when held up before light. In the distal ileum the mucosal surface was interrupted by numerous transverse ridges with granular surfaces (Fig. 1). The colon throughout its length was similarly affected but to a much greater degree. Its mucosa was coarsely granular with discrete 1-2 mm greyish nodules, and the transverse ridging was so striking that it appeared as coarse mucosal folds. The changes extended into the rectum. When segments of colon and distal ileum were held up so that light could penetrate the viscus wall, the ridging was seen to follow the course of small, thick-walled arteries. *Bone*—The trabecular pattern was normal. The marrow was very cellular and from it large amounts of reddish-grey material could be expressed. There were no lytic lesions in the sternum or vertebrae. The *adrenals* and *thyroid* were grossly normal.

#### *Microscopic Autopsy Findings*

*Skin*—Amyloid was distributed in muscle walls of subcutaneous vessels and questionably in the connective tissue of the epidermis and cutis vera. *Heart*—There were nodular deposits of amyloid in the subendocardium of both sides of the interauricular septum and the left auricle (Fig. 2). The medium and small intraventricular branches of the coronary arteries everywhere contained amyloid in the muscular walls (Fig. 3) and there were focal areas of myocardial degeneration and fibrosis in both ventricles. Amyloid could not, however, be demonstrated with certainty in the ventricular muscle itself. *Lungs*—Edematous and congested with focal areas of atelectasis. There was extensive amyloidosis in the pulmonary vessels and many scattered foci of deposition in the alveolar septa. *Spleen*—Extensive amyloidosis in blood vessel walls. There were plasma cells and some myeloma cells in the venous sinuses and in the red pulp. There were no diffuse amyloid deposits. *Liver*—Plasma cells were conspicuous in the sinusoids. There was central lobular congestion and amyloid deposits were found in the arteries of the portal fields. *Kidneys*—There were focal interstitial collections





FIG. 2. (15339) Infiltration of left auricular endocardium by amyloid

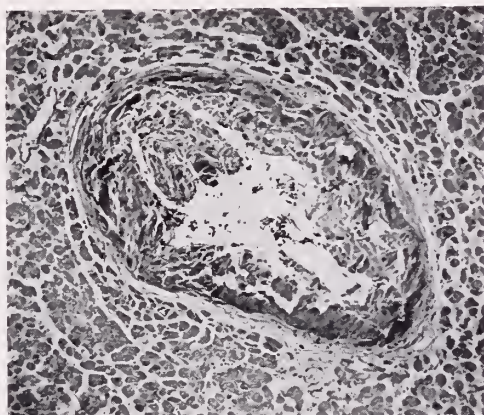


FIG. 3. (15339) Left Ventricle: Amyloid infiltration of an intramyocardial artery

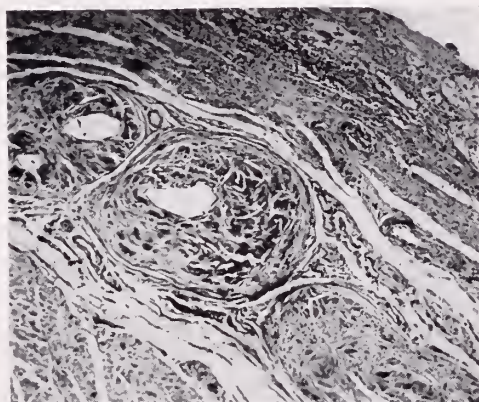


FIG. 4. (15339) Small Intestine: Arteries and veins of submucosa infiltrated by amyloid.  
200  $\times$



of lymphocytes with occasional plasma cells. Amyloid was deposited in the walls of small and large arteries but Bowman's capsules and the glomerula tufts were spared. There were, however, degenerative changes in the tubular epithelium with frequent protein casts. The tubules were not dilated. *Gastro-Intestinal Tract*—There was extensive deposition of amyloid in the walls of arteries and arterioles from the esophagus to the rectum (Fig. 4), in addition to which scattered foci of amyloid were found in both circular and longitudinal muscle coats of the distal small bowel and questionably so in the circular muscle of the colon. *Bone*—Some decrease in trabeculae. Marrow was cellular with diffuse increase in plasma cells.

Amyloid was also found in small and medium sized arteries of the ovary, bladder, tongue, breasts, thyroid, adrenals, pancreas and in the vasa vasorum of the aorta. There was no demonstrable amyloid in the cerebral arteries, though this has been reported elsewhere (9).

## CASE II

The patient, Y. S., was a 48 year old white housewife admitted to the Semi-Private Pavillion of The Mount Sinai Hospital because of progressive pain in the bony skeleton.

Except for recurrent episodes of bilateral phlebitis of 20 years duration, the patient had been in good health until four months prior to admission when she noted constant sharp sticking pain first in the right buttock and then in the left buttock and groin. These subsided spontaneously in a few days, but one month later similar pain developed in both scapulae, in the left lower rib cage and then in the right anterior chest. These symptoms persisted and were the presenting complaints on admission. The illness was associated with a 12 pound weight loss but there were no symptoms specifically related to the gastro-intestinal tract.

On examination the patient was an afebrile obese white female in considerable pain. Blood pressure 116/80, pulse 86, respirations 20. There was tenderness over the lower left lateral ribs, right anterior ribs, and over the lower dorsal and upper lumbar vertebrae. The lungs were clear and the heart was clinically unremarkable. The liver and spleen were not palpable. There was brawny edema of both legs with brownish cutaneous pigmentation, but no other abnormalities of the skin were evident. Neurological examination was negative.

*Laboratory.* Hgb. 13 gms, WBC 6,700, 69% segmented neutrophils, 7% non-segmented forms, 17% lymphocytes, 6% monocytes, 12% plasma cells. Platelets 100,000. Erythrocyte sedimentation rate 48 mm/hr. Urine—There was 1 plus albumin, but a positive HCl ring test was present and the Jacobson test for Bence-Jones protein was positive. Blood urea nitrogen 9 mg%, Albumin/Globulin ratio 4.2/2.6 gm %, phosphorus 3.9 mg%. Sternal and iliac crest marrow aspirations revealed numerous clusters of atypical plasma cells. X-rays of the skeleton showed all the bones to be riddled with small and large rounded sharply demarcated areas of bone destruction in addition to numerous rib fractures and partial compression of the vertebral bodies of L1, D5 and D8. There was also considerable generalized osteoporosis.

*Course.* The patient was begun on a regimen of urethane, up to 6 grams per day without improvement. The drug was discontinued after a week because of nausea and vomiting, and ACTH, 100 mg per day, was started with sufficient symptomatic relief to enable her to return home. She remained improved for three months until ACTH was stopped, and during the next several weeks experienced rapidly progressive severe generalized pain in the back, ribs, arms and fingers for which she was subsequently rehospitalized.

Examination at that time disclosed generalized tenderness of the skeleton with inability to move the extremities because of severe pain. She had developed a firm rubbery 0.5 cm cutaneous nodule in the right parietal region of the skull and a 3 to 4 cm area of irregular induration in the lower half of the left breast. The fingers had become swollen and spindle-shaped. Liver and spleen were still not palpable. The remainder of the physical examination was unchanged.

Laboratory tests now revealed Hgb. 8.5 gms, WBC 7,150 with normal differential. Platelets 230,000. Urine: Specific Gravity 1.010-1.015, albumin 1 plus but the HCl ring and Jacobson tests were again positive. The urinary sediment contained occasional white blood cells and coarse granular casts. Blood urea nitrogen 26-70 mg %, uric acid 8 mg %, Albumin/Globulin ratio 3.5/2.5 gm %, calcium 11.9 mg %, phosphorus 4.1 mg %, alkaline phosphatase 12 King-Armstrong Units. Bone survey showed a very large number of destructive lesions throughout the entire skeleton except the bones of the forearms, and the previously observed vertebral body compressions were again noted. Multiple pathological fractures of ribs were present bilaterally.

The patient was treated with transfusions, 1 mc of  $P_{32}$  on two occasions, and was finally given pentamidine, 150 mg intravenously q.o.d. for 6 doses. There was slight symptomatic improvement, but another course of pentamidine was without effect. In addition to the debilitating bone pain, the patient complained of anorexia, frequent eructations, intermittent nausea, vomiting and abdominal cramps. On several occasions peristaltic rushes were heard. There was a ten day period of obstipation resistant to laxatives and enemata. Because of these symptoms the presence of intestinal amyloidosis was postulated.

It was concurrently observed that the skin lesions were increasing, with progressive nodularity of the subcutaneous tissues of anterior chest and abdomen and with the appearance of discrete nodules 0.5 cm in size on the inner aspect of the left arm. A biopsy of such a nodule revealed the presence of amyloid deposits in the subcutaneous tissues.

The symptoms referable to the gastro-intestinal tract and osseous systems persisted. Shortly before death spontaneous clonus of the legs developed with hyperactive reflexes and positive Babinskis. The patient then rapidly deteriorated and finally died after five months of hospitalization.

#### *Gross Autopsy Findings (Incision was confined to the abdomen)*

The body was that of a well developed obese white female weighing 190 pounds and measuring 152 cm in length. The skin of the lower anterior thorax, of the inferior aspects of both breasts and of the upper abdomen was remarkably firm with a raised coarse, confluent nodularity. The epidermis was intact but could

not be moved freely over the nodules. Similar though smaller 0.5 cm discrete nodules were present on the inner aspect of the left arm and in the left axilla. When the abdominal incision was made, the panniculus adiposus was seen to be somewhat lusterless, and in the cutis vera of the upper abdomen there were many pale, tannish-yellow poorly delineated nodular areas. The body hair was normally distributed. In the proximal third of the right femoral shaft there was a fracture so complete that circumduction of the distal segment was possible. Palpation of the ribs revealed numerous easily depressed, crepitus areas and there was a 1 cm circular defect in the right frontal bone. The *heart* was not enlarged. The serous surfaces, chambers, valves and coronary arteries presented no grossly unusual features with the exception of the left auricular endocardium which was thickened and grey, with its smoothness interrupted by a fine, translucent granularity. The thickness was particularly marked in the interauricular septum where, just above the foramen ovale, there was a protuberant, semi-rigid, translucent limbus. The *lungs* exuded moderate amounts of edema fluid from the cut surfaces and there were focal areas of atelectasis in the basal segments of both lower lobes. *Spleen* weighed 190 grams. The capsule was smooth and transparent but the cut surface had a striking granular glistening appearance. *Liver* weighed 1450 grams. There was the diffuse "nutmeg" pattern of chronic passive congestion. *Pancreas* and *adrenals* were grossly unremarkable. *Genito-Urinary System*—The *kidneys* weighed 100 grams each. The corticomedullary junctions were poorly defined and the cut surfaces were quite pale. The bladder was grossly normal. The uterus contained many 2-5 cm intramural fibromyomata, but the internal genitalia were otherwise unrevealing. *Bone*—The trabecular pattern in the vertebral bodies was distorted by numerous punched out circular lesions which replaced the bony substance with gelatinous greyish-red material. The first lumbar vertebra was collapsed to such a degree that the anterior lips of the intervertebral discs lay in virtual apposition. Segmentally distributed along the courses of many ribs were areas in which the cortex was paper-thin, frequently fractured, and encasing soft red, hemorrhagic material. Segments of striated muscle removed with the ribs were remarkably firm, pale tan and waxy in appearance. *Gastro-Intestinal Tract*—The upper two thirds of the esophagus were not unusual, but in the lower one third the mucosa was wrinkled and nodular and the wall rigid, apparently due to remarkable thickness of the muscularis which on section had a peculiar pale, tan waxy appearance. The gastric serosa was covered with numerous pinpoint granules resembling dewdrops. Larger nodules, some several mm in size, were sporadically scattered throughout the stomach wall and many gastric vessels contained hard discrete nodules. The wall of the entire small bowel was strikingly rigid and scattered throughout its entire extent were many 1-3 mm. nodules many of which lay beneath valvuli conniventes, making these folds firm and immobile. A larger 0.5 cm nodule was found just proximal to the ampulla of Vater and many of the smaller nodules were associated with mesenteric vessels as they entered the bowel wall. In the colon similar firm collections lay beneath the mucous membrane which was particularly elevated and nodular in the descending colon and

rectum. In the distal rectum there was a 2 cm ulcer penetrating to the muscularis. The Valves of Houston stood out prominently and could not be effaced. The mesenteric fat was generally pale, yellowish-grey and occasionally remarkably firm. The appendices epiploicae were thus involved to a remarkable degree. The serosal surface of the entire bowel, especially the distal portion of the small intestine was greyish, finely granular and lusterless.

#### *Microscopic Autopsy Findings*

*Skin*—Discrete and confluent deposits of amyloid in the connective tissue of the subcutaneous fat. *Thoracic Skeletal Muscle*—Densely infiltrated with amyloid which was deposited in connective tissue septa around individual muscle fibers. *Heart*—There were nodular infiltrations of amyloid beneath the left auricular endocardium and scattered foci were distributed in the epicardial fat and in the connective tissue septa around muscle fibers of the left auricle and both ventricles (Fig. 5). *Lungs*—No stainable amyloid in vessels or alveola septa. *Spleen*—The reticulum of the red pulp was infiltrated with focal and confluent areas of amyloid some of which was in Malpighian corpuscles. *Liver*—No stainable amyloid in the parenchyma or vessel walls. *Pancreas* and *Adrenals*—negative. *Kidneys*—The tubules were grossly dilated and contained eosinophilic staining casts which took up congo red and iodine green stains. Foreign body giant cells were adjacent to many of the casts. Amyloid was deposited in the walls of an occasional artery but none was demonstrated in glomeruli. *Bone*—Marrow infiltrated with plasma cells. *Gastro-Intestinal Tract*—In the mesenteric fat, amyloid was deposited in delicate septa among the fat cells, and calcium was found in small globular clusters. In the esophagus, there were extensive amyloid deposits in connective tissue of the submucosa and muscularis. There was extensive amyloidosis of the entire muscle coat of the cardia with focal and confluent involvement of the muscular wall of the remainder of the stomach. The wall of the pylorus was virtually replaced by amyloid which extended extensively into the duodenum where there were, in addition, nodular subserosal

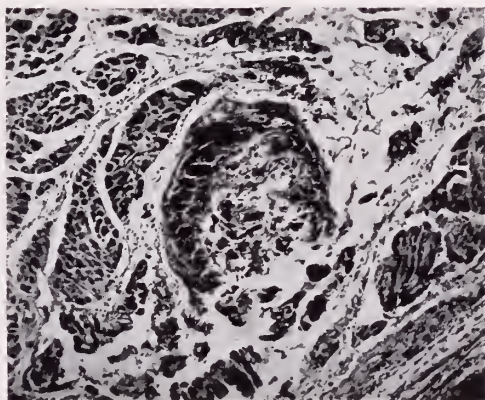


FIG. 5. (15428) Ventricular myocardium infiltrated by amyloid



collections. There were confluent foci of amyloid in both circular and longitudinal muscle coats of the entire ileum and jejunum penetrating from serosa to submucosa. The vessels of the submucosa were extensively involved. In the colon there were diffuse, nodular deposits of amyloid in the entire muscular coat. Vessels in adjacent mesenteric fat contained amyloid deposits in their walls.

#### DISCUSSION

The points of interest in these two cases lie principally in the nature, the extent and the clinical sequelae of the amyloidosis of skin, heart, and gastrointestinal tract. They are presented together because in many ways they supplement each other in emphasis.

The signs and symptoms of systematized amyloidosis can offer the clinician a sufficient index of suspicion to permit an accurate antemortem diagnosis. Usually the presenting features of the afflicted patient are those which first establish the presence of multiple myeloma, as in Case II in which the initial complaints were referable to the bony skeleton. Occasionally, however, the presenting symptomatology is provoked by the amyloidosis, as in Case I in which the patient was hospitalized with complaints chiefly referable to the heart. In both cases a histologic diagnosis was made by recognizing the skin lesions of systematized amyloid. In one case the diagnosis had been already established by biopsy of the gingiva (5).

In the "secondary" amyloidosis typified by that associated with antecedent chronic suppurative disease, involvement of the integument is most unusual, but in systematized amyloidosis, both "primary" and that associated with myeloma, recognition of cutaneous manifestations can be diagnostic (10, 11). These lesions can appear as hemorrhagic areas of varying size and occasionally as extensive purpura. The pigmentary changes are probably due to heme pigments. Translucent, waxy, spherical or flat-topped nodules simulating vesicles are also generally described (9-11). Different from these translucent papules are the subcutaneous nodules which may vary from small, discrete movable lesions to large pedunculated tumors, as in the case of Wolfram quoted by Goltz (11). Diffuse infiltrations of the skin vary considerably in extent but may result in thick, inelastic, yellowish transformation of the integument, especially about the head and neck. In Case II of this paper Y. S. initially developed typical discrete nodular cutaneous lesions on the scalp and in the breast. Two months later at autopsy the involvement had progressed remarkably, so that the skin of the lower anterior thorax, the inferior aspects of the breasts and the entire upper abdominal wall was a sheet of gross, confluent nodularity. In addition there were many 0.5 cm discrete nodules on the left upper extremity and in the axilla.

In 1929 Lubarsch (12) reported a case of unusual cutaneous amyloidosis in which loss of body hair was described. In 1952 Goltz (11) recorded the case of a 65 year old woman in whom "hair loss was striking" and in whom "the scalp, eyebrows, axillary and pubic hairs were sparse." In case I of this paper, R. S. had almost complete absence of body hair except for eyebrows and cranial vertex. Though a biopsy of the right forearm was unrewarding, scalp biopsy revealed

amyloid in the stroma around hair follicles and sebaceous glands. In addition there was extensive amyloidosis of the subcutaneous vessels at autopsy. A hyaline-like substance was found in the connective tissue of some areas of the epidermis and cutis vera, but stains for amyloid were at best questionable. The same patient R. S. had a patchy, erythematous, maculopapular skin eruption which began on the dorsum of the hands, then spread to the trunk and face and finally became generalized. The lesions were pruritic and there was considerable excoriation. In a case reported by Engel and referred to by Goltz (11) the patient showed "a livid erythema on the ears, cheeks and dorsal hands", and in one of Macdonald's (10) cases local redness of the skin was described. Usually, however, the symptoms referable to the skin are conspicuously absent, even with considerable involvement such as the patient in Case II, although itching, from moderate to severe in degree, has been recorded (11). Nevertheless, it is not possible to make a convincing etiologic comment about these erythematous lesions in Case I.

Neither patient displayed any grossly evident lesions of the tongue or mucous membranes, although in Case I amyloid was present microscopically in the arteries of both tongue and gingiva and in the gingival connective tissue.

In the case of "mollities ossium" published in 1872 by Adams and Dowse (2), the authors failed to recognize the association of the bony lesions and "the lardaceous changes" in the viscera. Askanazy (13) in 1904 reported the first recognition of this association and in his case the principal deposits of amyloid were in the muscle wall of the small intestine. Six years later Hueter (14) reported a similar case in which the patient had stubborn obstipation. Randall's (14) patient had the classic symptoms of mechanical intestinal obstruction and at laparotomy the "wall of the small intestine was greatly thickened and contained whitish deposits." At autopsy amyloid was confined particularly to the circular muscle of the small bowel. Milder symptoms such as diarrhea, abdominal pain, nausea, vomiting and constipation have been observed (14). A patient described by Golden (15), in which extensive deposits of amyloid were found in both small and large intestine, manifested not only preterminal intestinal atony but earlier in the course of the disease had steatorrhea. The same patient presented with massive hematemesis. At autopsy two greater curvature gastric ulcerations were found and amyloid in the walls of vessels near the bases of these ulcers was presumed to be etiologically related to their development. Eisen (9) found several other reported instances of gastro-intestinal bleeding.

The gastro-intestinal amyloidosis of the two patients described in this paper is interesting both in distribution and in extent. R. S. in Case I had only scattered foci of amyloid in the muscular wall of the ileum, but the arteries and arterioles were involved in a most striking fashion so that from stomach to rectum they could be palpated and seen through the bowel wall as thick cords which often caused an unusual ridging of the mucosa especially in the colon. The patient had protracted anorexia, nausea, occasional emesis and constipation but no bleeding and no demonstrable ulcerations in spite of the pronounced vascular involvement. In Case II the patient's nausea, vomiting, cramps and 10 day period

of obstipation were sufficiently marked to suggest the correct antemortem diagnosis. At necropsy the entire gastrointestinal tract from the lower esophagus to the rectum was remarkably involved with both nodular and confluent amyloid deposits which in many areas, including the pylorus, segments of small bowel and colon, virtually replaced the wall from serosa to submucosa. There was also extensive involvement of vessels, and in the distal rectum a 2 cm penetrating ulcer was found. There had been no clinical evidence of bleeding.

In 1856, eight years after Virchow described amyloid, a paper appeared by Wilks (16) in the Guy's Hospital Report. According to Kerwin (17) this was the first recorded case of cardiac failure associated with the deposition of amyloid in the myocardium. The most frequent sequel of cardiac amyloidosis is slowly progressive heart failure (9, 17, 18). There may be mild to pronounced cardiomegaly and occasional arrhythmias especially auricular fibrillation and premature ventricular systoles (9, 19). Although congestive cardiac failure is common, angina pectoris appears to be distinctly rare. Dillon and Evans (20), in 1942 described a single case associated with primary amyloidosis. It is of considerable interest, therefore, that the patient in Case II had as one of her presenting complaints typical symptoms of angina pectoris. At autopsy the heart weighed 360 grams (normal approximately 300 grams) and was dilated, soft and flabby. Careful examination of the coronary arteries revealed relatively few flexible subendothelial plaques none of which narrowed the vascular channels. Microscopic examination disclosed amyloid involving the walls of small and medium sized intramural arteries. There were focal areas of myocardial degeneration and fibrosis in the walls of both ventricles, but amyloid could not be demonstrated with certainty in the ventricular muscle itself. Binford (21) reported a case of primary amyloidosis in which the myocardium and the small divisions of the coronary arteries were extensively involved, but the patient displayed only congestive failure without angina pectoris. In both cases in this paper, there were fine, translucent, punctate deposits of amyloid in the endocardium of the auricles which appears to be a site of predilection (15, 19, 22). Amyloid was not demonstrated in the coronary arteries in Case II, although it was focally distributed in the epicardial fat, in the muscular wall of the left atrium and in the wall of both ventricles.

#### SUMMARY

Two cases of systematized amyloidosis associated with multiple myeloma are reported. Both patients were females of middle age (48 and 54 years). The cases are considered to be of particular interest because of the unusual cutaneous, gastrointestinal and cardiac manifestations.

One patient displayed extensive confluent nodular involvement of the integument which was asymptomatic. The other displayed a striking loss of body hair. Though the coincidence of the alopecia and the cutaneous amyloidosis found in this patient may be taken as evidence of an etiologic relationship, such a conclusion must be made with reservation.

In Case I the amyloid was found in the walls of arteries of every organ examined

including the vasa vasorum of the aorta. The cerebral vessels were the only exceptions. This patient displayed both angina pectoris and congestive heart failure and at autopsy was found to have insignificant coronary artery arteriosclerosis, but amyloid was demonstrated in the intramyocardial vessels. It is suggested therefore, that the clinical manifestations of heart disease might have been directly related to the deposition of amyloid in the smaller radicals of the coronary arteries.

Both patients had gastro-intestinal amyloidosis, one principally of blood vessels, the other of both blood vessels and intestinal musculature from esophagus to rectum. In this patient the amyloid sufficiently compromised the functional activity of the bowel so that symptoms of intestinal obstruction ensued.

The clinical and pathological similarity of primary systematized amyloidosis and the amyloid associated with multiple myeloma are again noted.

It should be emphasized that the amyloid observed in these cases was deposited in the interstitial connective tissue in such a fashion that the cellular structure was encapsulated and finally underwent compression atrophy and physical replacement as the amyloid increased in amount.

#### *Acknowledgment*

The author would like to thank Dr. I. Snapper for permission to use the clinical data in Case II.

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## MASCULINIZING TUMOR OF THE OVARY: SUCCESSFUL TREATMENT OF AN ARRHENO-BLASTOMA<sup>1</sup>

GERTRUDE FELSHIN, M.D. AND BERNARD BERGLAS, M.D.

Hormone producing or functional ovarian tumors have been recognized for many years as clinical and pathological entities. The literature on this subject is voluminous, however most of the reports are of small groups of cases followed over an inadequate period of time. Novak (1) emphasizes this fact and he thinks that this explains the differences of opinion as to the pathology, histogenesis and degree of clinical malignancy of these tumors. The term arrhenoblastoma was coined by Meyer (2) for a group of ovarian tumors that originated from the vestiges of dormant testicular elements persisting in the ovary. These tumors often have defeminizing and masculinizing effects. Microscopically they show an architecture suggestive of testicular elements. Meyer has demonstrated the close histogenetic and pathologic relationship between the various types from the highly differentiated type originally described by Pick (3) as tubular testicular adenomas through the intermediary group to the diffuse undifferentiated varieties.

The follow-up of the case to be presented has reached the stage of complete clinical restitution to normalcy as evidenced by successful pregnancy and delivery of a normal child following the removal of a masculinizing arrhenoblastoma of the ovary.

### CASE REPORT

M. R. (#6846) 31 year old married white female was admitted to the gynecological service of The Mount Sinai Hospital, March 17, 1953 because of sterility of 11 years duration. Menarche began at 14 years of age and menses, occurring every 28-34 days and lasting 5 days with moderate flow, ceased at the age of 26 years. Her previous history was non-contributory except that she had had an appendectomy in 1950.

At the age of 25 years the menses became irregular and one year later stopped. A diagnostic curettage performed in another hospital in 1949 was reported as "negative". Soon thereafter the patient noticed an increase in hair growth and in 1951 she applied for treatment at the endocrine clinic of the gynecological service of The Mount Sinai Hospital. The physical findings were those of a well developed female with increased hirsutism of face and body. The breasts appeared well developed but flabby and there was a male type of distribution of pubic hair. There was a slight acne of the face and back. No abdominal striae were noted. The gynecological findings were as follows: nulliparous vaginal introitus, clitoris appeared slightly enlarged, the vagina and vaginal portion of the cervix were normal, the uterus was anteverted, firm and freely movable, anteflexed and normal in size, the parametria on both sides were soft and non-tender and

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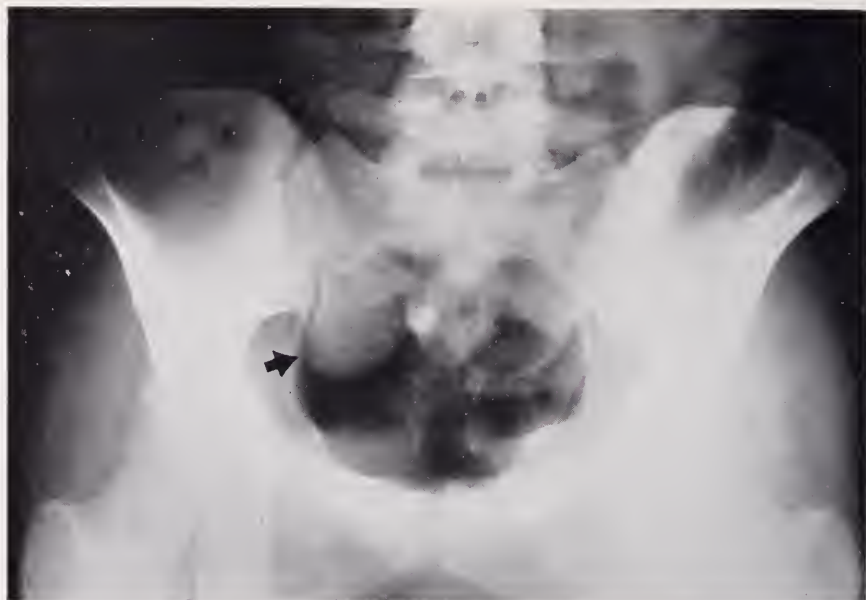


FIG. 1

the tubes and ovaries could not be felt. No masses or tenderness could be determined on palpation. Laboratory work-up: BMR minus 6%, serum blood cholesterol 220 mgm. % iodine<sup>131</sup> excretion 45% (normal), serial vaginal smears continued over many months showed marked estrogenic deficiency without cyclic variation; there were many basal cells and leucocytes present as seen in a menopause smear. Repeated endometrial biopsies showed atrophic endometrium or "scant tissue, insufficient for diagnosis". X-ray of the sella turcica was normal. Examination of the eye fundi and visual fields were normal. Intravenous pyelogram was normal and showed no displacement or distortion of the kidney pelvis. Perirenal insufflation showed normal roentgenological findings. Determination of 11 oxy-steroids and 17 keto-steroids showed normal values (1.0 mgm. and 13.1 mgm. respectively). Urinary gonadotropins were decreased. (Negative at 90 mouse uterine units; negative at 45 mouse uterine units; negative at 30 mouse uterine units; negative at 5.5 mouse uterine units; normal is 6-50 mouse uterine units.)

These findings suggested a syndrome of defeminization and slight masculinization in a young woman. At first the laboratory findings did not indicate the etiology. During the course of observation and study in the gynecological clinic it was noted that the masculinizing signs were increasing. The hirsutism increased, the voice deepened, the body contours lost their female characteristics and the clitoris was increased two to three times the normal size. On repeated gynecologic examinations it was noted that the right ovary became more readily palpable. These findings justified hospitalization for surgical exploration, and accordingly the patient was admitted to the Mount Sinai Hospital. The physical

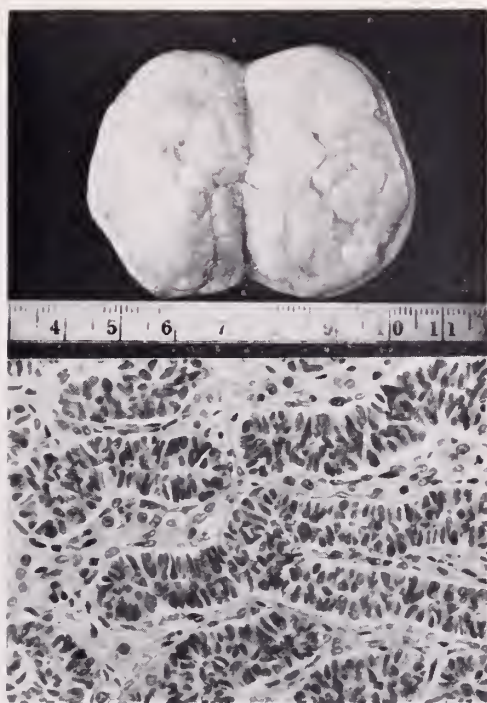


FIG. 2

findings were confirmed and gynecography was performed by insufflating 1000 cc of CO<sub>2</sub> into the peritoneal cavity by tubal insufflation. This revealed an enlarged right ovary (Figure 1).

On March 23, 1953 a laparotomy was performed through a Pfannenstiel incision and the right ovary was found to be replaced by a yellowish, smooth, glistening freely movable 3 x 4½ x 3 cm. tumor which was removed. The uterus and left tube and ovary were normal. The post operative course was uneventful.

The histologic report was: Arrhenoblastoma of the ovary.

Microscopically "The tumor consists mainly of epithial cells forming irregular trabecular network without lumina. The tumor cells are oval in shape, hyperchromatic, and rather regular. No mitotic figures are seen. The fibrous stroma contains a few large lipoid containing cells, these closely resemble the Leydig cells of the testicle" (Figure 2).

As early as April 22, 29 days post operative, the patient had a normal menstruation following 5 years of amenorrhea. The menstruation continued at 28 day intervals and lasted 3-4 days with moderate flow until August 1953 when the menstruation ceased due to pregnancy.

The pre-natal course was entirely uneventful and on May 5th, 1954 at The Mount Sinai Hospital she was delivered by low forceps of a normal 6 pound 8½ ounce girl by Dr. Irwin Wiener.



## COMMENT

Defeminization and masculinization in a female during the reproductive period present a striking clinical picture. The signs of defeminization were amenorrhea, regression and atrophy of the breasts, and loss of the typical rounded female contours of the body. The masculinization of the body was evidenced by increased hirsutism, deepening of the voice and the enlargement of the clitoris. These symptoms had developed in a woman who previously had normal secondary female sex characteristics. This has to be borne in mind because many of the masculinizing features found in females present congenital or genetic characteristics of the individual and are not due to the presence of a masculinizing tumor.

There are 4 types of tumors that may produce masculinization of the female:

1. The arrhenoblastoma
2. Certain adrenal tumors
3. Masculin ovoblastomas
4. Hilus cell neoplasm

The laboratory findings in this case showing a deficiency in estrogen production, a decrease of urinary follicle stimulating hormones, a decrease of the urinary output of 17 keto-steroid fraction, in addition to the negative IVP and negative peri-renal insufflation were helpful in ruling out adrenal neoplasm as a cause of the masculinizing syndrome. The clinical impression of an ovarian etiology of the masculinizing syndrome was based upon the slight enlargement of the right ovary confirmed by gynecography. The presumptive diagnosis of arrhenoblastoma of the ovary was confirmed by operation and the pathological examination of the removed tissue.

## SUMMARY

1. Differential diagnostic steps in determining the etiology of masculinizing tumors in the female are described.
2. The pre-operative diagnosis of arrhenoblastoma was made.
3. Complete regression of the masculinizing effects was achieved by operation.
4. Pregnancy and delivery of a normal living baby present a clinical restitution to normal.

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## BENIGN TUMOR OF THE URETER<sup>1</sup>

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The diagnosis of primary ureteral tumor is no longer a urological rarity. The number of reported cases of primary ureteral malignancies is steadily increasing, indicating a greater awareness of the occurrence of these lesions. Since the great majority of reported cases concern malignant tumors, the occurrence of a primary benign tumor of the ureter seems sufficiently interesting to warrant the detailing of the following case.

### CASE REPORT

K. L., a 25 year old white man, was first seen on 9/8/50. He gave a history of having had an attack of severe left back and flank pain with radiation anteriorly, three months prior to this visit. He was hospitalized at another institution where X-rays were said to have shown a small left ureteral calculus. Shortly after admission to that hospital, the patient spontaneously passed a small stone, and was discharged. Soon thereafter, the patient had a second attack of left sided colic and was re-admitted to the same hospital. X-rays and cystoscopy done at this time were said to have shown no calculi, but a dilated left kidney was found. No operation was advised, and the patient was again discharged. When he began to have recurrent dull left sided pain, he sought further advice. There was no history of chills, fever, or hematuria associated with these attacks of pain. On further questioning, the patient remembered having had similar attacks at the age of 8 or 9 years. Except for a right sided pleurisy 5 years prior to this visit, his past history was essentially negative.

Physical examination revealed a healthy appearing, well developed young man in no acute distress. Complete examination revealed no abnormalities. There was no costovertebral tenderness and no masses were palpable. Urinalysis was negative chemically and on microscopic examination showed a few red cells per high power field.

On 9/11/50 an excretory urogram was done (Fig. 1). No radiopaque calculi were visible on the preliminary film. After intravenous administration of contrast substance there was prompt bilateral upper tract visualization. The right upper tract appeared entirely normal. The left kidney was considerably hydro-nephrotic. On no film was the left ureter seen and on a 3 hour film there was considerable trapping in the left pelvis.

The patient was referred to The Mount Sinai Hospital where he was admitted on 10/1/50 with a diagnosis of either nonopaque ureteral calculus, or ureteropelvic stricture.

Physical examination again revealed no definite abnormalities. Preliminary laboratory studies were as follows: Urine, acid, albumin 0, sugar 0, microscopic

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FIG. 1

few white blood cells; hemoglobin, 15 grams; white blood cells, 13,900, segs. 73, non-segs. 14; lymphocytes 10; monocytes 3; blood urea nitrogen 10 mgm %; blood Wasserman was negative; blood sugar 70 mgm %; blood type A, Rh negative; X-ray of the chest showed inactive tuberculosis of right upper lobe.

On 10/2/50, under spinal anesthesia, cystoscopy was performed. The bladder and ureteral orifices appeared normal. A catheter was passed the full distance into the left pelvis without obstruction and specimens of urine were obtained for culture, acid-fast studies and Papanicolaou stains. These tests were subsequently reported as negative. The ureter catheter was removed and a bulb ureteropyelogram was done. The films showed a relative narrowing at the ureteropelvic junction with considerable hydronephrosis (Fig. 2) and almost complete trapping (Fig. 3).

The admission diagnosis was not altered, and exploration was performed on 10/20/50. Under spinal and pentothal anesthesia the left kidney and ureter were exposed extra-peritoneally through a lumbar muscle-splitting incision. The kidney was found to be quite dilated and the parenchyma thinned. The ureter was mobilized to the uretero-pelvic junction. No calculi were palpated and there was no extra-ureteral compression. A small ureterotomy was made at the ureteropelvic junction, whereupon a long, worm-like structure popped out of the incision. The ureterotomy was increased and four more worm-like projections were discovered. These were all seen to arise from one fairly narrow stalk (Fig. 4). The



FIG. 2



FIG. 3





FIG. 4

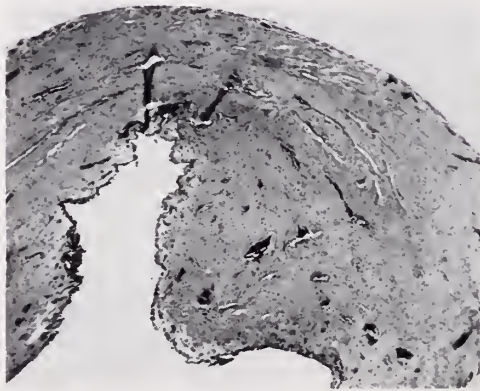


FIG. 5

lesion appeared grossly benign, but because of the advanced hydronephrotic atrophy of the kidney, nephrectomy and excision of as much of the ureter as possible was carried out.

The post-operative course was entirely uneventful, and the patient was discharged on 10/29/54, the eighth postoperative day.

The pathology report was "Left kidney and ureter showing fibro-epithelial

polypi in the ureter 4 cms from the pelvis, at the site of a slight constriction showing chronic non-specific inflammation. There is hydronephrosis and chronic pyelitis." A low-power magnification of one of the polyps shows its benign nature (Fig. 5). The patient has remained well since the operation. When last seen in Oct. 1952, he had no complaints and urinalysis was entirely negative.

#### DISCUSSION

Primary ureteral tumors are rare lesions and the great majority of these are malignant. Of the benign types the most common are papillomatous in nature, and the least common are those which consist principally of stromal elements covered by essentially normal epithelium. Excellent reviews of this subject have been presented by Scott (1), Vest (2), Martinsen and Murphy (3), and Senger and Furey (4).

The benign nature of the reported tumor was recognized at the operating table and the question of local excision and ureteral anastomosis was raised. In this particular case, nephrectomy and partial ureterectomy was decided upon because of the existing advanced hydronephrosis and infection. The controversial subject of local excision of benign ureteral tumors was raised by Vest (2) in 1945 when he reported three cases of "benign" tumors of the ureter treated by local resection and ureteral anastomosis or repair. Since many pathologists believe that all ureteral tumors are potentially malignant, this method of treatment must be accepted as dangerous, since there are reported cases of death from metastases after local excision of so-called benign ureteral tumors.

#### SUMMARY

A case of benign ureteral tumor, fibro-epithelial polyp, is presented. The disease manifested itself by ureteral colic and hydronephrosis and was treated by nephrectomy and partial ureterectomy.

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## STUDIES IN MYASTHENIA GRAVIS: CARDIAC AND ASSOCIATED PATHOLOGY<sup>1</sup>

HARVEY MENDELOW, M.D.,<sup>2</sup> AND GABRIEL GENKINS, M.D.<sup>3</sup>

Although the symptomatology of myasthenia gravis was first described in 1672 by Willis, the disease was recognized as a clinical entity only in the nineteenth century by several investigators, Oppenheim in particular. His monograph, published in 1901, based on sixty cases, remains the classical description.

Myasthenia gravis is now defined (1) as a chronic disease characterized by variable generalized weakness and rapid fatigability following the use of voluntary muscles, particularly those of ocular movement, facial expression, deglutition and speech, and commonly the trunk and limbs. The respiratory muscles are involved in the most serious cases. Cardiac and smooth muscles are generally assumed to be unaffected. Clinical progress of this disease may be slow, and punctuated by numerous relapses and spontaneous remissions, but may also be severe and fulminating. The characteristic response to prostigmine and similar drugs, used both as a diagnostic test and as a means of therapy, is well known. Cases with fatal termination usually display progressive resistance to drug therapy, with ensuing respiratory paralysis and its complications.

The anatomic pathology of this disease however, remains obscure and variable in nature. For example, several fatal cases have been reported without any definite major postmortem abnormalities. This situation led to the application of the term "bulbar paralysis without anatomic changes" in the older literature. To this day, no one theory of the pathogenesis of this disease has gained universal acceptance.

The generally recognized features of its pathologic anatomy follow: a). The so-called "lymphorrhages", or collections of lymphocytic cells found in skeletal muscle mainly, but also in adrenals, liver, thyroid, etc, and other internal organs. These are found in about two-thirds of the cases (2). b). Some abnormality of the thymus gland, in the form of either hyperplasia, or the presence of a benign or malignant thymoma. These abnormalities are seen in about one-half of the cases of myasthenia gravis (2-4). c) The existence of clinically undisputed cases of myasthenia gravis, as described above, in which no pathologic findings of note are present at autopsy.

Because of the paucity of anatomic data in this disease, we undertook to study the pathologic aspects of twelve consecutive cases of myasthenia gravis and/or thymoma, in which post mortems were obtained during the last five years. In general, these cases had been carefully investigated clinically,\* and it was hoped that some correlations between clinical and anatomic features might be es-

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tablished. Early in this study, we became impressed with the frequency with which myocardial lesions, in particular myocarditis, was encountered. We therefore have attempted to establish whether this myocardial alteration is an incidental finding or an integral part of the pathologic anatomy of myasthenia gravis.

#### CASE REPORTS

*I. R. L.*—30 year old white female. Four months history of progressive diplopia, ptosis and dysarthria, with later respiratory difficulty and increasing refractoriness to prostigmine. EKG: Depressed ST segments in leads 1, 2. Depressed T in 1, 2, 3. T<sub>4</sub> inverted. Normal cardiac outline on X-Ray. Death in respiratory failure.

*Post Mortem*—pulmonary atelectasis and focal bronchopneumonia. Thymus—persistent, 25 grams. Heart—Gross, left ventricular hypertrophy. Micro., neg. Skel. muscle—rare focal lymphocyte collections.

*II. G. K.*—49 year old white female. Onset with mild weakness and rapid progression to fulminating “bulbar” type of myasthenia gravis over two week period. Thoracotomy for “persistent thymus”. EKG: neg. Stormy P. O. course with respiratory failure and death in spite of prostigmine therapy.

*Post Mortem*—pulmonary atelectasis and edema. Thymus—hypertrophic, removed surgically. Heart—Gross, dilatation of all chambers. Micro., mild interstitial fibrosis. Skel. muscle—rare lymphorrhages.

*III. R. L.*—41 year old white female. Polio at age two with residual right arm and left leg paresis. Five month history of left hand weakness progressing to “bulbar” paralysis, with marked dysphagia. Some relief from one treatment with prostigmine. Diagnosis not made clinically. Died in coma with convulsions.

*Post Mortem*—chronic pulmonary congestion with stasis infarcts. Thymus—neg. Heart—Gross, right ventricular hypertrophy. Micro., focal myocardial atrophy with fiber vacuolization and interstitial lymphocyte and mononuclear infiltration. Skel. muscle—extensive waxy degeneration and focal fibrosis and calcification, with mild chronic inflammatory reaction. (Psoas).

*IV. R. S.*—37 year old white female. Admitted with diagnosis of anterior mediastinal tumor. Exploratory thoracotomy revealed malignant thymoma. X-Ray therapy given. One month P.O. developed weakness, fatigue, dysarthria, and dysphagia. Died suddenly on third day of admission, with no specific therapy having been given.

*Post Mortem*—pulmonary edema. Thymus—malignant thymoma with lung invasion and pleural metastases. Heart—Gross, normal. Micro., extensive areas of myocardial necrosis with inflammatory reaction of polys, lymphocytes and multinucleate giant cells. Skel. muscle—one small section taken shows similar focal necrosis and inflammatory reaction.

*V. E. A.*—43 year old white female. Six month history of progressive fatigue, dysarthria and dysphagia. Only fair prostigmine response, but Tensilon test unequivocally positive. Anterior mediastinal mass noted on chest X-Ray examination. Repeated episodes of respiratory failure unresponsive to massive prostigmine and OMPA therapy, but partially relieved by IV Tensilon. EKG: neg. Death in respirator.

*Post Mortem*—Atelectasis and bronchitis. Thymus—malignant thymoma with lung invasion and metastases to pleura and diaphragm. Heart—Gross, normal. Micro., focal myocardial necrosis. Acute and chronic inflammatory reaction, mainly diffuse and interstitial in character. Skel. muscle—rare focal necrosis and lymphorrhages.

*VI. E. W.*—51 year old negro male. Mediastinal mass found on routine X-Ray examination of chest. Responded to ACTH and X-Ray therapy with decrease in size, but recurred. Exploratory thoracotomy revealed malignant thymoma with extensive pleural metastasis.



Continued ACTH therapy caused marked shrinkage in the size of the mass, and of the pleural nodules, but patient developed a Cushing syndrome. Cessation of ACTH therapy was followed by onset of typical myasthenic syndrome, with dramatic response to prostigmine. Symptoms kept under control by use of cortisone and prostigmine but the institution of cortisone apparently caused increased resistance to prostigmine, with eventual death in respiratory failure.

*Post Mortem*—Thymus—malignant thymoma with metastases to pleura bilaterally. Heart—Gross, flabby myocardium with mottled yellowish and reddish gray areas. Micro., severest extensive myocardial necrosis, with abundant inflammatory reaction by polys, lymphocytes and mononuclears. No myocardial region is spared. Skel. muscle—comparable extensive severe necrosis with clumping and fragmentation of fibers and removal from sarcolemmal sheaths. Similar acute and chronic inflammatory reaction. All muscles examined display identical changes.

VII. A. S.—47 year old white male. History of occasional weakness, ptosis, and dysphagia over a nine year period, with no limb involvement, and good response to prostigmine in low dosage. Loss of responsiveness during period of renal colic, with multiple episodes of respiratory failure. At first some success with ACTH therapy was achieved, but this failed later, as did use of OMPA. Controlled for short period with prostigmine, guided by repeated Tensilon tests for dosage levels, but finally succumbed.

*Post Mortem*—Bilateral lower lobe atelectasis. Thymus—neg. Heart—Gross, normal. Micro., small collections of lymphocytes but no muscle necrosis. Skel. muscle—same.

VIII. A. B.—65 year old white female. Eight month history of progressive weakness, dysarthria, dysphagia and weight loss. Physical and laboratory examinations not contributory. Admission diagnosis: Carcinoma of esophagus. Tensilon or prostigmine test not done. Sudden death on evening of admission.

*Post Mortem*—Thymus—benign encapsulated thymoma. Heart—Gross, old rheumatic valvulitis. Micro., areas of hyaline and perivascular fibrosis. Foetal myocardial necrosis and acute inflammatory reaction, with mild interstitial myocarditis. Skel. muscle—focal lymphorrhages.

IX. F. N.—54 year old white male. One year history of generalized weakness culminating in dysphagia and respiratory difficulty, necessitating tracheotomy one month prior to admission. Admitted for control of myasthenia. EKG: Sinus bradycardia. Biphasic T in AVL. ST segment elevated V1-6; some response to parenteral prostigmine, but death in coma and convulsions while in respirator.

*Post Mortem*—Acute pulmonary congestion and edema with pleural effusions and bronchopneumonia. Thymus—neg. Heart—mild interstitial fibrosis. Skel. muscle—neg.

X. M. B.—27 year old white female. Known epileptic since age two, controlled on dilantin. One and a half year history of weakness, ptosis, and dysarthria. Treated with OMPA due to poor response to prostigmine. Following respiratory crisis, underwent thymectomy (slightly hyperplastic thymus removed). After this, frequently required use of respirator. Treated at Mount Sinai Hospital with combined therapy of Mestinon and prostigmine, but finally died in respiratory failure.

*Post Mortem*—Lower lobe atelectasis bilaterally. Thymus—hyperplastic, surgically removed. Heart—Gross, normal. Micro., extensive foci of fibrosis, mainly subendocardial in left ventricle, some showing recent granulation tissue and chronic inflammatory reaction. Skel. muscle—neg.

XI. M. W.—19 year old negro female. History of myasthenic symptoms for seventeen months with initial good response to pyridostigmine. Later very unstable to therapy, and episodes of respiratory failure ensued during one of which she suddenly died.

*Post Mortem*—pulmonary edema. Thymus—neg. Heart—Gross, normal. Micro., mildest diffuse interstitial myocarditis with no muscle necrosis. Skel. muscle—focal atrophy, but no necrosis.

XII. J. A.—22 year old white female. Severe hyperthyroidism since age of fourteen. Several courses of Radioiodine for therapy, surgical treatment being considered too risky.

Three months typical history of myasthenia gravis symptoms with initial response to prostigmine, later becoming refractory to this drug. Admitted in severe respiratory failure and died in respirator, despite all therapeutic measures.

*Post Mortem*—Tracheobronchitis and extensive atelectasis, Graves disease. Thymus—neg. Heart—Gross, right ventricular hypertrophy. Micro.,—focal fibrosis. Skel. muscle—neg.

#### DISCUSSION

It may be seen from the descriptions of the histopathology in the twelve cases presented above, that some histologic alteration of the myocardium is a prominent feature of this series, being present in at least six of the twelve cases. This alteration appears as foci of myocardial necrosis of all degrees of severity. These range from scattered focal atrophy and vacuolization of the myofibrils, with accompanying slight lymphocytic infiltration of the connective tissue septae (resembling lymphorrhages) in cases III and XI, to the severest, extensive myocardial necrosis. This latter is accompanied by abundant inflammatory reaction, consisting of polymorphonuclear leucocytes, lymphocytes, and mononuclear cells, with occasional multinuclear "giant" cells. This form is exemplified by cases IV and VI (Fig. A, C). In addition, case X presents the unusual picture of numerous areas of myocardial fibrosis, some of which are still moderately vascular and infiltrated with small numbers of chronic inflammatory cells, and iron-containing macrophages. These areas resemble the later stages in the repair of an area of myocardial necrosis, familiar to us in the form of a healing myocardial infarct (Fig. D). One might tentatively relate this change to a late stage of the severe forms of myocardial necrosis described above, but one must await the occurrence of other illustrative cases before such conclusions are drawn.

This high incidence of myocardial necrosis and inflammation in our series therefore appears to represent not just a coincidental finding, but possibly a basic feature of the pathology of myasthenia gravis. Examination of the literature brings to light several scattered case reports which seem to substantiate this conclusion.

Weigert, in 1901, was the first to report microscopic lesions of the myocardium in a case of thymic tumor with myasthenia gravis. He noted collections of cells infiltrating the myocardium and epicardium, which he thought to represent metastatic growth from the thymoma (later disproven, since this tumor was one of those now classified as benign) (5). Buzzard (5), in 1905, also reported "lymphorrhages" in the myocardium of two of his five cases of myasthenia gravis. Similarly in 1921, Bouttier and Bertrand (5) noted considerable cardiac muscle edema and fiber dissociation, with interstitial infiltration by chronic inflammatory cells in one reported case. Barton and Branch (6), in 1937, described a case of myasthenia gravis with extensive interstitial myocardial infiltration by lymphocytes, macrophages, and occasional polymorphonuclear leucocytes, with edema and fragmentation of myocardial fibrils.

However, the first investigators to express the opinion that myocarditis is an integral part of the pathology of myasthenia gravis were Rottino et al. (5), who reported a case with thymoma and diffuse myocardial necrosis with acute and chronic inflammatory reaction, almost identical in appearance to our cases

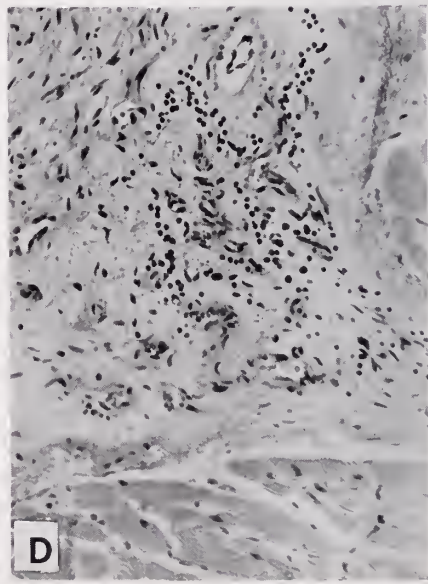
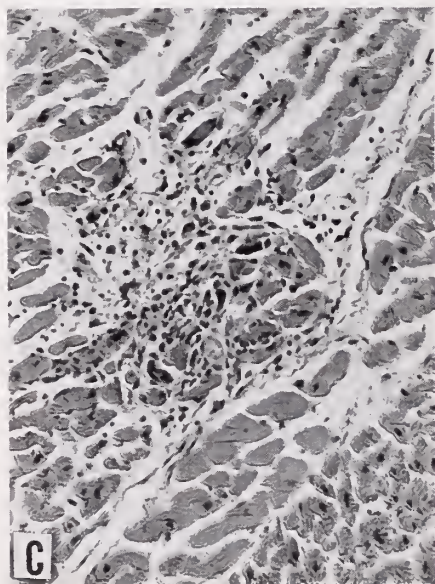
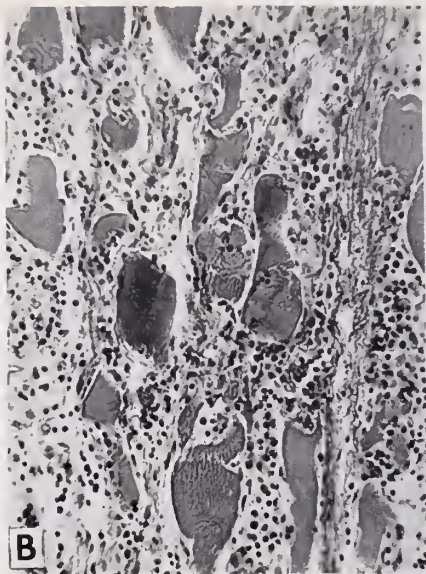
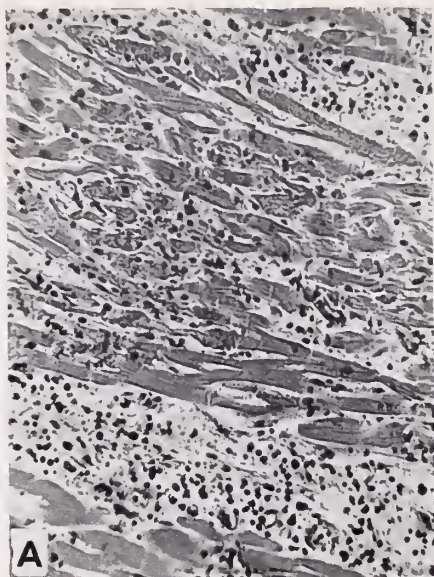


FIG. A. (left) Myocardium, Case VI. Necrosis and acute inflammatory reaction  
FIG. B. (right) Striated Muscle, Case VI. Myositis. Note the similarity to Fig. A  
FIG. C. (left) Myocardium, Case IV. Myocarditis similar to that seen in Case VI, Fig. A  
FIG. D. (right) Myocardium, Case X. Focal myocardial fibrosis, still moderately cellular and vascular.



IV and VI. A very similar case, also associated with thymoma, was reported by Giordano and Hammond (7), and two other cases, again with thymoma, were described by Brem and Wechsler (8). In addition, Russell (9), in a study of the striated muscle lesions of myasthenia gravis (eight cases) noted focal myocardial necrosis and inflammatory reaction in three of six cases in which the cardiac muscle was studied microscopically.

Myocarditis as such is not a rare condition. It is encountered incidentally as a post-mortem finding, with a wide range of frequency in reported series, depending principally on how carefully the heart was examined microscopically (10). It is also a well known aspect of the pathology of numerous disease entities, particularly those of infectious nature, hypersensitivity reactions, the so-called "collagen diseases", etc. In addition it is occasionally found as an isolated, unsuspected cause of death in apparently healthy individuals (as in the granulomatous, or "Fiedler's myocarditis").

However, it is interesting to note that in the several large series of cases carefully investigated by Saphir and others (10), myasthenia gravis and/or thymoma is never noted as a possible cause of, or in relation to, myocarditis. In a tabulation of the diseases associated with 1400 cases of myocarditis studied at the Armed Forces Institute of Pathology, myasthenia gravis is not even listed, although only forty-three cases were all that remained as "idiopathic" in nature in their classification.

The apparent discrepancy of these findings with the high incidence of myocarditis encountered in our series and reported in the literature of myasthenia gravis, seems well resolved by the comments of Rottino et al. (5). In a careful survey of all the reported cases of myasthenia gravis since 1901, they note that in a large proportion of these, the heart is either not mentioned, or described as grossly normal but without microscopic confirmation. In addition, one of the features of this lesion of the myocardium is its scattered, spotty distribution, and variation in severity even in the same case. Therefore, one or two routine sections of the heart might easily miss the involved areas of the less severe cases.

Another feature of the series of cases presented here is the parallelism between the cardiac lesions and those of the striated muscle, both as to type and degree of severity (also see Russell (9)). The classical small "lymphorrhage" as the only pathologic feature of the striated muscle involvement, is supplanted in at least four of these cases by actual necrosis of muscle fibers with secondary inflammatory reaction of varying intensity. In case VI for example, where the cardiac lesion was most severe, sections of striated muscle from all areas of the body displayed a pathological picture almost identical to that seen in the myocardium (fig. B). This suggests some possible kinship in pathogenesis in this disease, by which both cardiac and striated muscle are similarly affected. Evidence in support of this concept is again found by reference to the case reports in the literature. In the cases studied by Giordano and Hammond (7), Barton and Branch (6), and in Russell's series (9), the striated muscle presented a prominent picture of necrosis, edema, and secondary inflammatory reaction, some with areas of



Zenker's waxy degeneration, and multinucleated "giant cells", far in excess of the usually reported "lymphorrhages".

This concept of an identity of pathogenesis was investigated clinically by Taquini et al. (11). Careful study of fourteen cases of myasthenia gravis with respect to the clinical status of the cardiovascular system and its reactivity to mecholy, atropine, carotid sinus pressure, etc. did not reveal any abnormal responses. In addition, the authors report that the post-mortem examination of one of their cases displayed no unusual gross or microscopic findings. They concluded that the neuromuscular mechanisms affected in striated muscle were not comparable to those of cardiac muscle. Our own series showed no clinical aberrations of the cardiovascular system during life (including unchanged electrocardiograms in some patients with definite myocarditis later demonstrated pathologically). However, it must be mentioned that thorough clinical evaluation and EKG examination of cardiac status was not performed in all our patients, due mainly to the certainty of the clinical diagnosis during life.

Some clinical observers (1) have expressed the opinion that myasthenia gravis, or more properly, "the myasthenic syndrome", may not be a single disease entity, but a group of closely related conditions. They cite as evidence for this concept the difference of clinical course and behavior of cases with and without thymoma, as well as the types of myasthenic syndromes encountered in association with hyperthyroidism, and in some states of malnutrition etc. The variability of response to prostigmine and other drugs, the different rates of progression of the disease, and the presence or absence of frequent exacerbations and spontaneous remissions are all arguments in favor of such a separation. We might consider the presence of a terminal myocarditis as perhaps another distinguishing feature of one of these sub-groups. In fact in our series, a definite relationship between the existence of a thymoma, benign or malignant (but particularly malignant) and ensuing myocarditis may be noted (see Table). The four cases

#### SUMMARY OF PATHOLOGIC FINDINGS

Case No.	Thymic Abnormalities	Cardiac Lesions (Particularly Myocardial Necrosis)	Skelet. Muscle Lesions
I R. L.	Persistent thymus	0	+
II G. K.	Persistent thymus	0	+
III R. L.	0	+	++ (old polio?)
IV R. S.	Malignant thymoma	++++	+++
V E. A.	Malignant thymoma	++	+
VI E. W.	Malignant thymoma	++++	++++
VII A. S.	0	0	0
VIII A. B.	Benign thymoma	++	+
IX F. N.	0	0	0
X M. B.	Persistent thymus	Patchy fibrosis	0
XI M. W.	0	0	0
XII J. A.	0	0	0

0-++++—to indicate degrees of severity of lesion described.

in this series with thymoma all revealed myocarditis at post-mortem, and the severest cases of myocarditis were all in the thymoma group. Similarly, in the reported cases of myocarditis gravis in the literature six out of eight cases were associated with thymoma. The confirmation of this correlation must still await future reports of the pathology of myasthenia gravis cases with and without thymoma, with special reference to myocardial alterations.

#### SUMMARY

A study of the pathological findings encountered in twelve consecutive cases of myasthenia gravis and/or thymoma, with special reference to myocardial lesions, is presented. The pertinent literature is reviewed.

1) Myocardial necrosis with secondary inflammatory reaction is found to be an integral part of the pathology of myasthenia gravis, in this series, with particular frequency in those cases associated with thymic tumors.

2). The observations of Russell and others that striated muscle lesions may be of much greater severity than the usual reported "lymphorrhages" is confirmed. In addition, in those of our cases with the most severe cardiac lesions, striated muscle necrosis and secondary inflammation was of a comparable degree of severity.

3). The value of more intensive clinical study of the cardiac status in patients with myasthenia gravis and/or thymoma is suggested, and careful histopathologic study of the heart muscle in post-mortem examinations in this disease appears indicated. Comparison of skeletal and cardiac muscle lesions may reveal a common pathogenetic factor.

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# THE ELECTRICAL RESPONSE OF THE CEREBRAL CORTEX TO CORTICOPETAL IMPULSES: A COMPARISON OF PERIPHERAL AND CONTRALATERAL CORTICAL STIMULATION\*

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In most previous reports of the electrical response of the cerebral cortex to stimulation either of the cortex itself or of pathways leading to the cortex, at least two discrete elements were described. The first is usually relatively brief, relatively constant in amplitude and form (with constant stimulus), and with relatively brief latency and brief refractory periods. It seems to be more independent of depth of anaesthesia and of degree of spontaneous cortical activity. The second component, on the other hand, shows sensitive variation in latency, voltage, form and duration with degree of anaesthesia and amount of spontaneous cortical activity. Compared to the first element, the latency and refractory periods of the second response are relatively long. The first element is usually ascribed to the approach or the first synaptic passage of the afferent volley arriving at the cortex. The second element is usually ascribed to a reverberation in cortico-thalamic or intracortical circuits. Descriptions of the first element that have appeared in the literature, have been fairly consistent. On the other hand, descriptions of the second element have not been entirely uniform, and indeed, some authors have spoken of more than one component in the second element itself. Forbes and Morison in describing the electrical response of the cortex to afferent stimulation proposed the term "primary discharge" for the first element and "secondary discharge" for the second (21). This terminology will be used in this paper in describing electrical response of the cortex to afferent stimuli, to contralateral cortical stimuli, as well as to local cortical stimulation.

In 1936, Bishop spoke of an instantaneous cortical response to optic stimuli and of a repetitive response (5). The repetitive response exhibited the same frequency as spontaneous electrical activity (in the rabbit), namely 5 per second. In 1939, Forbes and Morison described a widespread electrical response of the cortex to stimulation of the sciatic nerve during deep barbiturate anaesthesia, and as mentioned above, they termed this response the "secondary discharge" (21). They did not observe a secondary discharge during ether anaesthesia. The secondary discharge was extinguished when stimuli followed each other more frequently than 3 per second and they usually required a one second rest period before they could again be elicited in full size. They found that the secondary discharge was absent if the stimulus came immediately after a spontaneous electrical wave. The primary response on the other hand was not decreased in amplitude as a result of rapidly repeating stimulation. They found the second-

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ary discharge in both hemispheres while the primary response was limited to the sensory receiving area of the contralateral hemisphere. In 1940, Bentley spoke of two cortical elements responding to visual stimuli (4). One element responded specifically to the visual stimulus while the second element appeared in later components of the response, which were, he believed, a manifestation of alpha rhythm.

In 1941, Adrian described in great detail the electrical response of the cortex to afferent stimulation in animals under the influence of different anaesthetics (1). The initial response under all circumstances was a surface positive cortical wave, ascribed by Adrian to potential gradients in the afferent fibers rather than to the activity of cortical neurones. This element was often followed by a surface negative wave which Adrian attributed to a discharge of impulses from cortical neurones. This second element was much more responsive than the first to convulsant drugs applied to the cortex as well as to interference of blood supply to the cortex. It was seen with animals under the influence of chloralose anaesthesia or moderate dial or nembutal anaesthesia. In deep dial or nembutal anaesthesia the primary response might be followed by a series of surface positive cortical waves which Adrian attributed to rhythmic after-discharges from the thalamus.

Marshall, Woolsey and Bard in 1941, described two kinds of secondary response (28). The first was encountered when there was a good deal of spontaneous cortical activity and its latency increased with the distance from the point of maximal response for the primary. The second was encountered when there was less spontaneous cortical activity and was quite similar to the secondary discharge described by Forbes and Morison (21).

Dempsey and Morison described three responses to stimulation of the sensory pathways whether in the radial nerve, the medial lemniscus, the thalamus or the thalamo-cortical radiations (17). The first was the usual primary response to stimulation at relatively high frequencies. This was followed by what they called an "augmenting sensory response". This response was absent after one stimulus but with repetitive stimulation increased in size gradually. The third component of the response was the "repetitive sensory response". This consisted of a train of 8-12 per second waves which followed the primary response to a single stimulus and which fatigued rapidly on repeated stimulation. There was no mutual blocking between the primary and augmenting responses or between the primary and repetitive responses although there was mutual blocking between the repetitive and augmenting responses. In the same year, Morison and Dempsey reported that augmenting and repetitive responses could be observed in the thalamus of a decorticated animal but that intact cortico-thalamic circuits reinforced these elements in both thalamus and cortex.

Jarcho, in 1949, demonstrated that the thalamo-cortical after-discharge, following a conditioning stimulus delivered to the sensory pathway, depressed the excitability of the sensory cortex with respect to a subsequent test shock as measured by the amplitude of the primary response of the latter (24). Forbes and his coworkers observed that increasing depth of anaesthesia and cooling



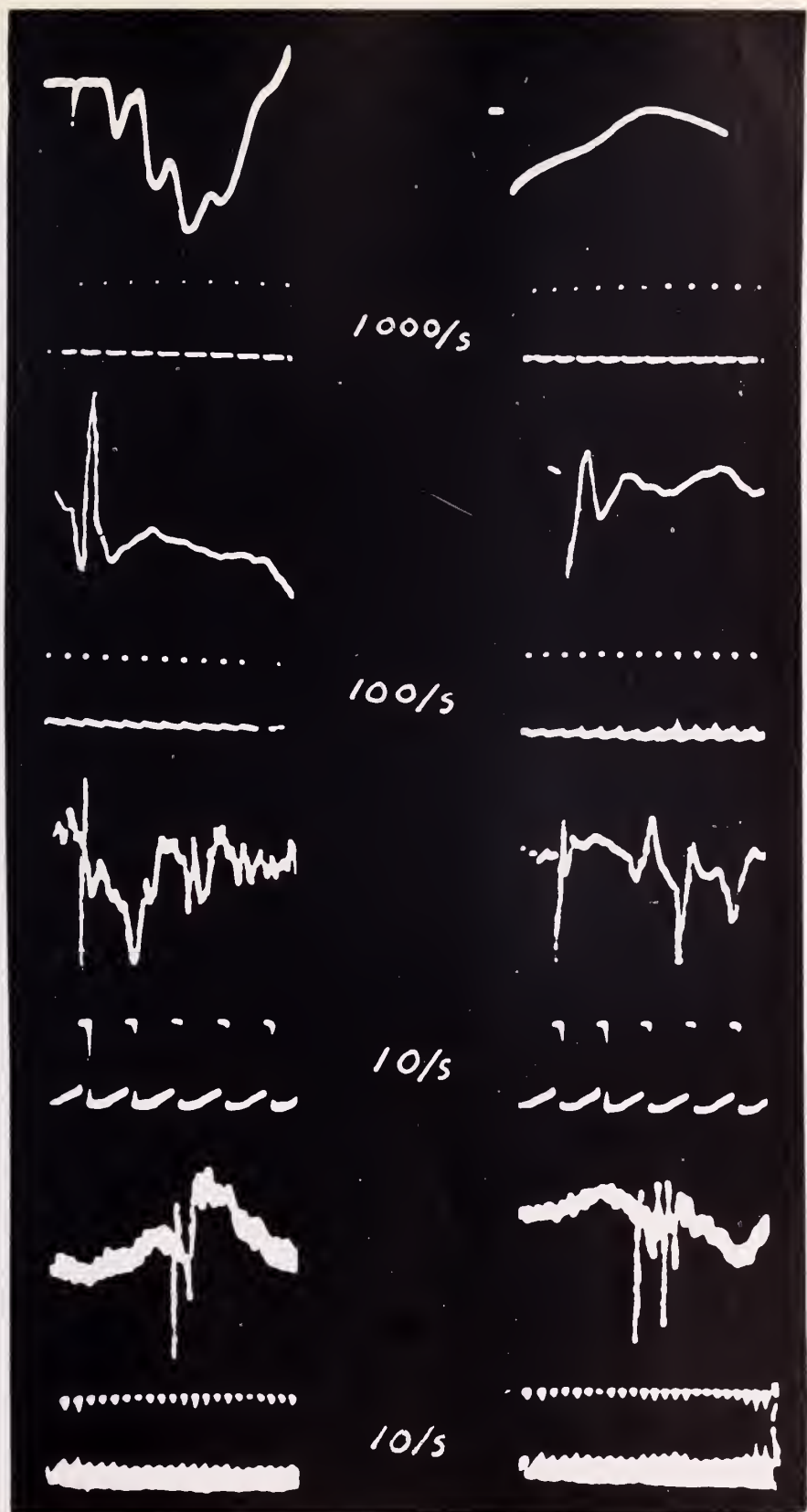
the brain increased the latency and the recovery time but decreased the critical repetitive frequency of the secondary discharge. Bremer and Bonnet described two types of repetitive response to sensory stimulation in the acoustic cortex of the cat (9). One they called the quick after-discharge and they encountered this either in the non-narcotized or the lightly etherized brain. The slow after-discharge appeared in moderate barbiturate anaesthesia or in the initial stage of anoxia or natural sleep. The latter they interpreted as the activity of cortical neurones in response to volleys of impulses discharged repetitively by thalamic and mesencephalic relay nuclei.

In 1950, Chang presented a detailed study of the repetitive discharge following sensory stimulation (12). He observed that repetitive discharges with a frequency of 10–12 per second could be observed as a result of stimulation of each sensory system. The discharge itself could be detected only in the primary receiving area of the modality stimulated. Destruction of either thalamus or cortex obliterated the response in both structures and therefore he inferred that this was a cortico-thalamic reverberation. Electrical stimulation of the cortex in the region at which the primary and repetitive responses were recorded, was able to elicit the same repetitive response though following a different primary response. Although Jarcho had interpreted his results as indicating that the afferent volleys and the reverberating impulses shared the same neural thalamo-cortical pathways, Chang inferred that they travelled in separate, non-interfering pathways. Chang also observed rhythmically fluctuating excitability of the sensory cortex as measured by the height of the primary response to a test stimulus. The fluctuations in excitability were synchronous with the repetitive response to the conditioning stimulus, as observed by Jarcho. Further confirmation was offered by Gastaut and his coworkers in 1951 (22).

The electrical response of the cortex to local stimulation has been studied somewhat less extensively. In 1936, Adrian reported that following a weak stimulus there is a surface negative response (1). When the stimulus was more intense, the local negative response was followed by a positive one. Under certain conditions an after-discharge followed. Adrian attributed the initial negative response to excitation of the neurones in the superficial layer of the cortex and the subsequent positive waves to cells activated some distance below the surface. Chang in 1951, confirmed Adrian's findings and ascribed the initial negative spike to activation of the apical dendrites of the cortical pyramids and he ascribed the longer lasting slow waves to the mass activity of intracortical neurones (13). He also found that he could reproduce the same cortico-thalamic reverberations obtained by stimulation of the sensory pathway, when he applied an electrical stimulus to the auditory cortex. In 1950, Burns made similar observations on neurally isolated slabs of cortical tissue remaining in situ with undisturbed circulation (10). The same author repeated his experiments in 1951 but this time in an unanaesthetized animal (11). His observations were similar

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FIG. 1 (left) and 2 (right). A comparison of the cortical response to peripheral (Proximal stump of spinal cord severed just below the foramen magnum) stimulation (left) and to contralateral cortical stimulation (right). The animal was prepared under ether anaesthesia which was discontinued after the cord was cut below the foramen magnum. The response is shown at four different sweep speeds.



FIGS. 1 AND 2

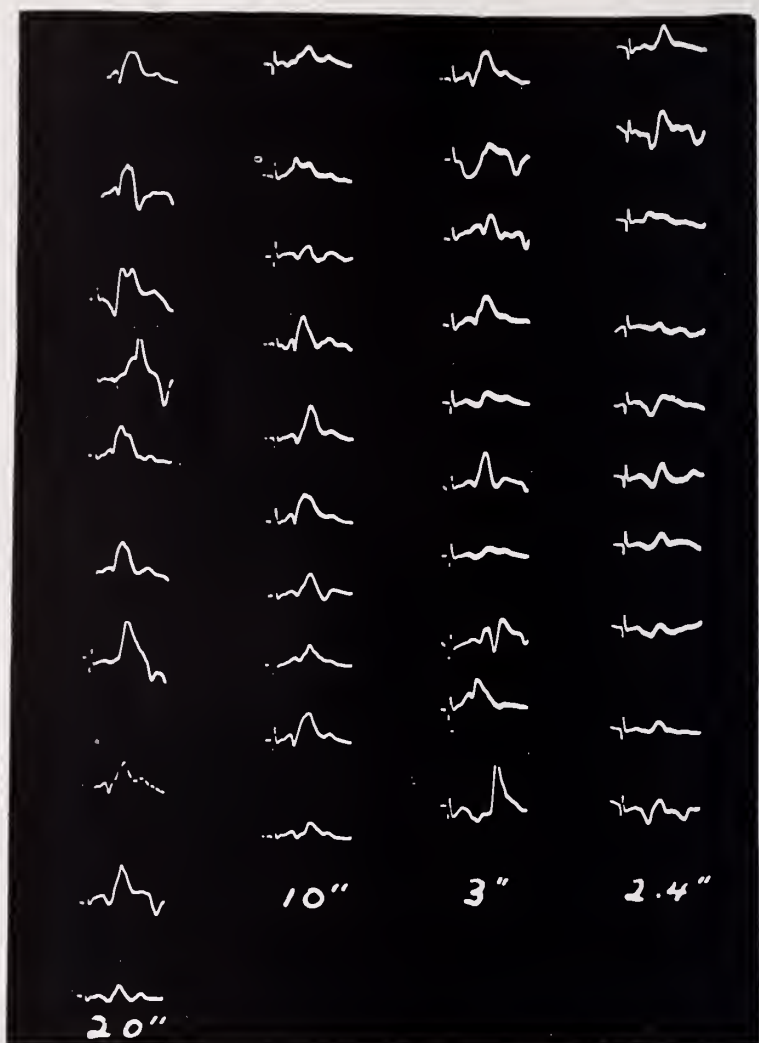
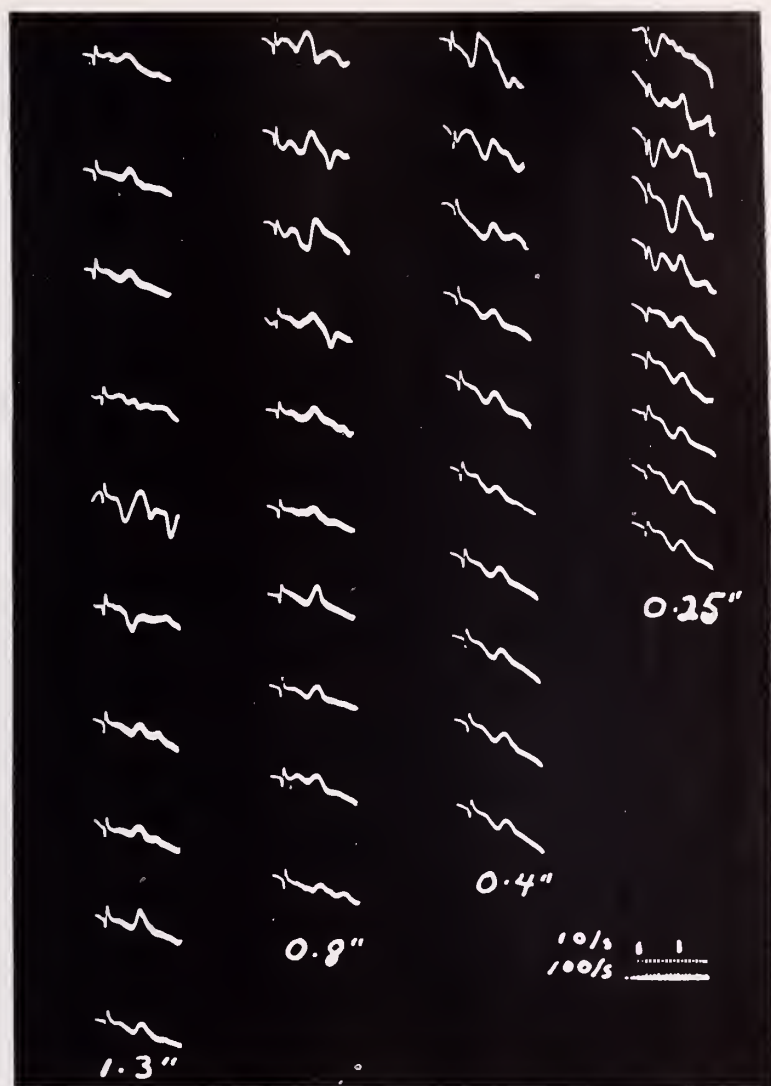


FIG. 3. The effect of frequency of stimulation on the cortical response to peripheral stimuli. Each column from above downward represents successive responses at intervals indicated. When the interval between successive stimuli is less than 1.0 second, the secondary response fatigues. Intraperitoneal nembutal was used during preparation and recording. The cortical response was picked up at the left cortex and the stimulating electrodes were on the right brachial plexus. Spontaneous activity is to be seen superimposed on the evoked responses.

except that following stimulation at one point, the electrical activity would continue for several minutes. Burns concluded that this was the consequence of self reexcitation in closed chains of neurones (11).

The electrical response of the cortex to stimulation of the contralateral cortex at a homologous point was described by Curtis in 1940. He ascertained that the corpus callosum was the pathway (16). The response, he said, was typically

FIG. 3, *continued*

diphasic with an initial surface positive component lasting about 15 milliseconds and a subsequent surface negative component lasting about 75 milliseconds. This second component was markedly reinforced by the application of a convulsant drug to the pia, obliterated by the application of nembutal or cocaine while the positive component was unaffected. Curtis concluded that the ascending volley was responsible for the positive wave while the descending volley was responsible for the negative wave.

It was the purpose of this investigation to compare the electrical response of the cortex to contralateral cortical stimulation with the response to peripheral



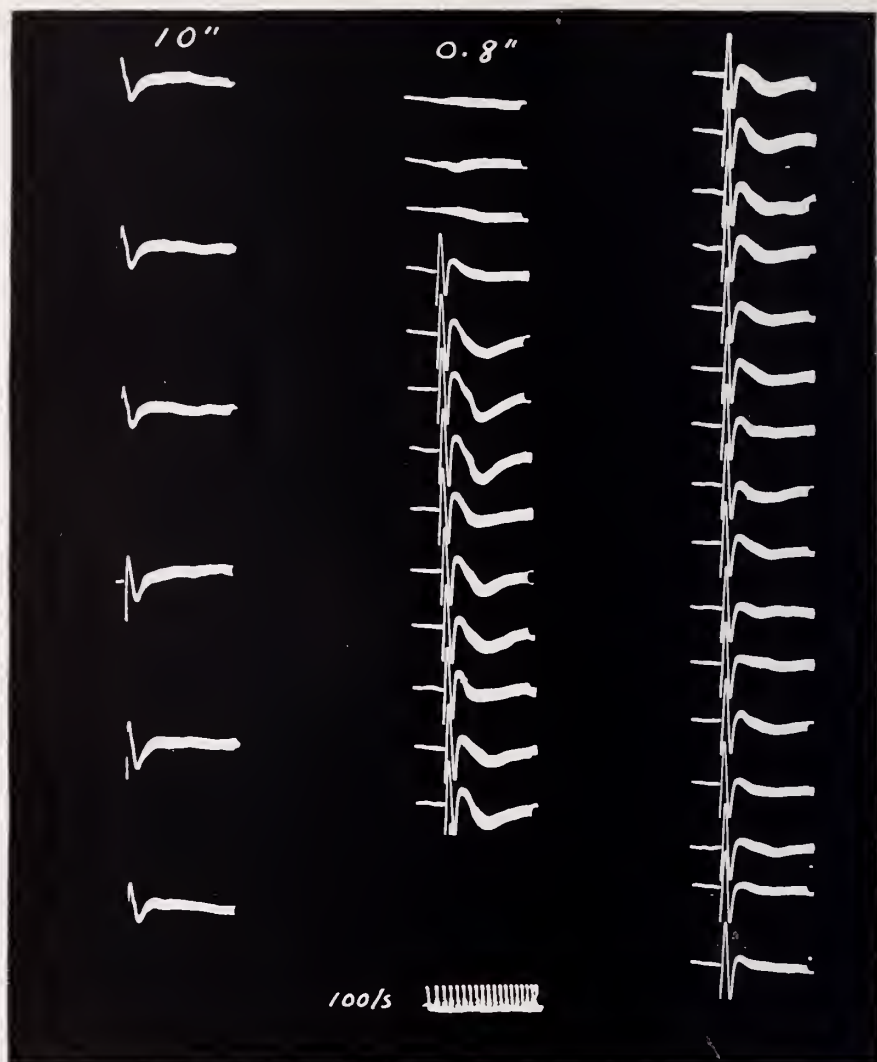


FIG. 4. The effect of frequency of stimulation on the secondary portion of the cortical response to contralateral cortical stimulation. When the interval between successive stimuli decreases to the order of 1 second, the secondary response (the upward deflection following the upward sharp spike) increases in amplitude within the first few stimuli and only later begins to fatigue. Intraperitoneal nembutal was used during preparation and observation. The interval between the successive responses appearing in the first column is 10 seconds; the interval between successive responses in the second and third columns which represent a continuous series, is 0.8 seconds.

sensory stimulation. Attention was directed chiefly to the relatively inconsistent, longer latency activity which is here termed the secondary discharge.

#### METHODS

Observations were made on 14 cats. In some cases intraperitoneal nembutal was used as anaesthesia. In other cases, ether was employed for the preparation

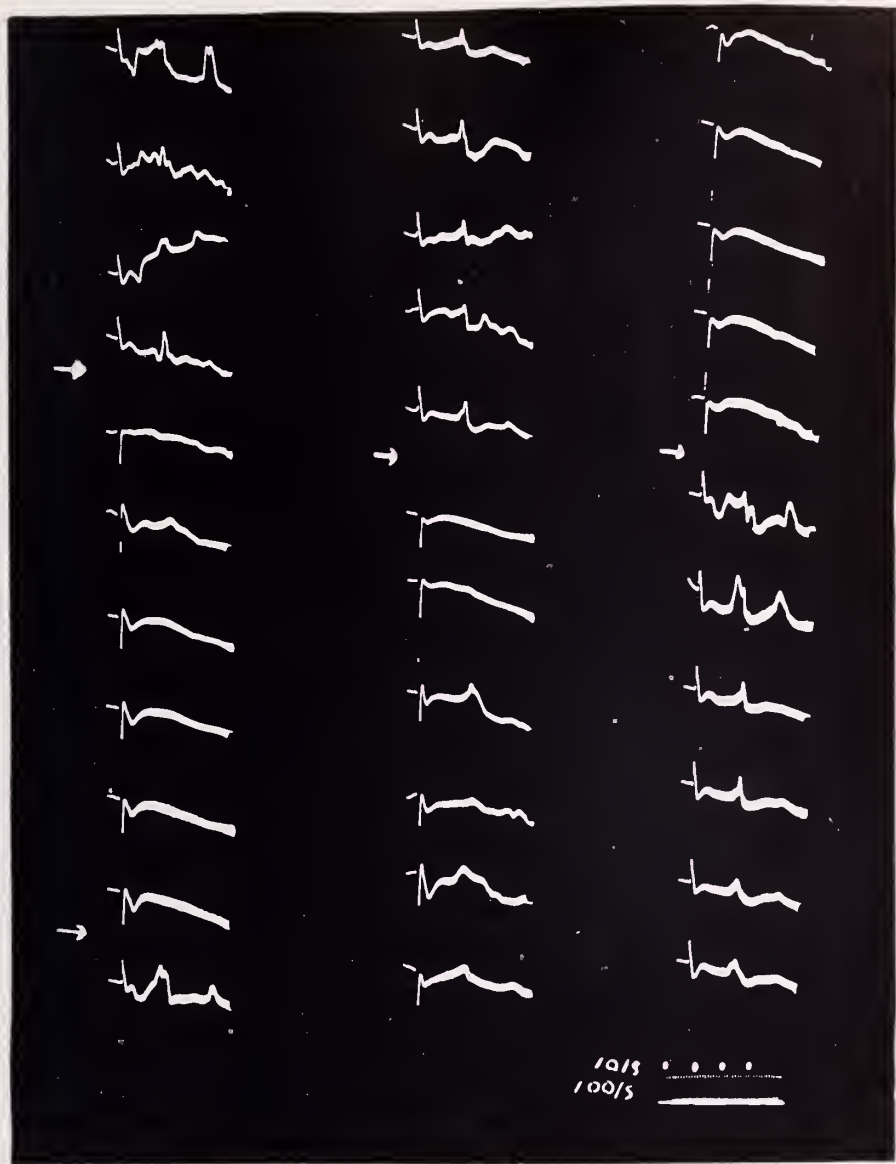


FIG. 5. A series of stimuli delivered every 0.8 seconds is provided to the right brachial plexus and to the right cortex alternately without breaking the rhythm of stimulation. The figure illustrates that the secondary response to stimulation of the right brachial plexus recovers from its fatigue even while the right cortex is being stimulated. Similarly, even during repetitive stimulation of the brachial plexus, the buildup of the response to cortical stimulation may be dissipated. The arrows indicate the point of changeover from one locus of stimulation to the other. This is the same experiment as that illustrated in figure 4.

but its administration was discontinued following section of the spinal cord at the foramen magnum (encephale isolé, Bremer 1936 (7)). In the latter cases, bipolar electrodes delivered electrical stimulation to the proximal stump of the spinal cord. In the former cases, electrodes delivered stimuli to the brachial plexus

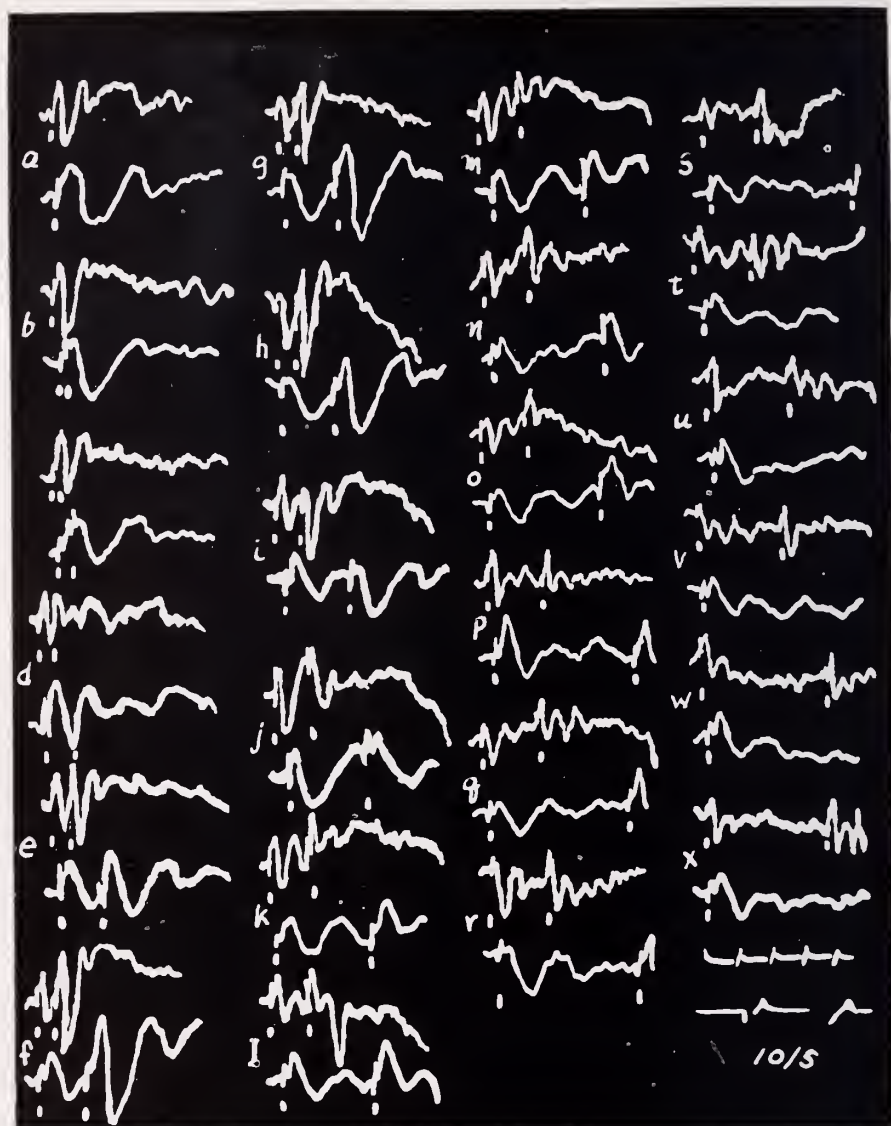


FIG. 6. Two successive stimuli are delivered at varying intervals to the proximal stump of the spinal cord severed just below the foramen magnum. The figure illustrates the gradual increase in the size of the second primary response and secondary response as the interval between the two stimuli increases. Moreover, the facilitation of the secondary responses to stimuli is observed when the interval between the two stimuli is such that the first wave of the second secondary occurs simultaneously with the second wave of the first secondary (f, g, h). The animal was prepared under ether anaesthesia which was discontinued when the cord was cut. Note that each response is given with slow sweep above and fast sweep below, as indicated by the time calibrations. The second stimulus comes in after the completion of the fast sweep in sample t and all below. The short vertical lines indicate the points of stimulation.

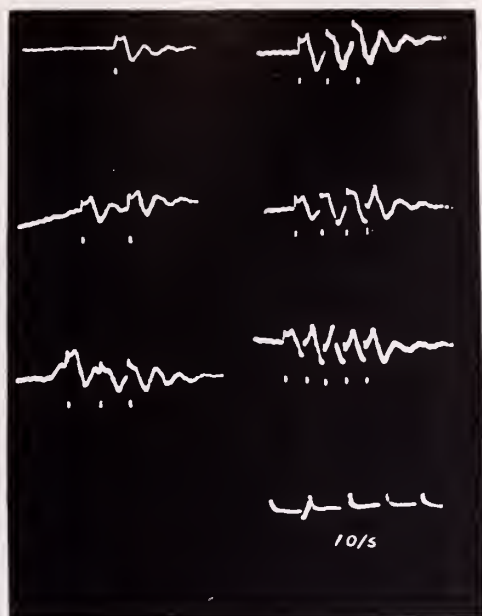


FIG. 7. With the tetanic stimuli applied to the cord at the proper frequency, facilitation of the secondary response can be elicited, i.e. driving occurs. The short vertical lines indicate each stimulus. These observations are taken from the same experiment as that illustrated in figure 6.

which was exposed for the purpose. Recording electrodes were placed so that one was anterior to the coronal sulcus and one a few millimeters posterior, upon the suprasylvian gyrus. Usually the activity of the left cortex was recorded while stimuli were provided to the right brachial plexus, to the proximal stump of the severed spinal cord or to the right cortex at a homologous point. Each recording electrode was a coiled silver wire, terminating in a smooth ball. One or two channels of amplification were used feeding into a single or double beam oscilloscope for photographic records. The amplifiers were highly differential and condenser coupled, with a time constant of 0.25 seconds or more.

## RESULTS

### 1. *Characteristics of the Response*

The characteristics of the cortical response to peripheral stimulation, that is, brachial plexus or cord stimulation, were consistent with those generally described in the literature. For example, in one case with cord stimulation, the primary response started at about one millisecond and continued for about 30 milliseconds. The secondary response followed immediately and lasted as long as half a second (Figure 1). In that same experiment, the response to contralateral cortical stimulation began within 0.5 milliseconds\* and continued for about 10–15

\* The beginning of the response is not clearly indicated in the illustration. However, other samples obtained with stimulus of opposite polarity exhibited the latency mentioned.



milliseconds. A secondary response began immediately after the primary and persisted for 0.5 to 0.7 seconds (Figure 2). The contralateral cortical response was recorded over a slightly wider area than the response to peripheral stimulation, but away from the point homologous to the point of stimulation the amplitude of the response fell off sharply. Moreover, although in the case of response to peripheral stimulation, the secondary response was more widespread than the primary, in the case of contralateral cortical stimulation, the secondary response was much less widespread than the primary response. Spontaneous bursts at about 10 per second when they occurred, were superimposed upon the primary and secondary of either type of response without evidence that the one form of activity interfered with the other.

## *2. The Response as a Function of Frequency of Stimulation*

In general with peripheral stimulation repeated as often as once per second the size of the secondary response was progressively reduced (Figure 3). The more frequent the stimulation, the greater the reduction in the size of successive responses. However, even with stimulation as frequent as 4 per second small deflections persisted. Usually when stimulation was provided once every ten or twenty seconds, no difference in the amplitude of successive responses was observed. The rate of decrease in the amplitude of the secondary response and the frequency at which the decrease became evident, varied from animal to animal, probably as a complex function of the stage of anaesthesia and the condition of the vital functions, among other factors. The decrease at high frequencies was somewhat obscured by the fact that frequent stimulation also obliterates spontaneous activity so that the response to stimulation may become more prominent though lower in amplitude.

By contrast, the secondary response to contralateral cortical stimulation was not decreased by successive stimulation at similar frequencies. In fact, it often happened that 2, 3, or 4 stimuli were required before the secondary response built up to its maximum height (Figure 4). With further stimulation, the amplitude of the response might fluctuate up and down.

In two instances, when peripheral stimuli were provided sufficiently frequent to obtain considerable depression of amplitude of the secondary response, stimulation was then transferred from the brachial plexus to the contralateral cortex at the same frequency and without breaking the rhythm. This secondary response built up as rapidly as usual to its maximum, and remained there. When stimulation was again abruptly switched to the brachial plexus it was found that the peripheral secondary had completely recovered (Figure 5). This experiment was repeated several times and in each case the brachial plexus secondary and the contralateral secondary behaved as though there were no mutual interaction.

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FIG. 8. As the interval between two stimuli delivered to the contralateral cortex increases, the cortical response to the second stimulus increases. In this experiment the second secondary response developed fairly abruptly. Its first appearance is indicated by the arrow. The short vertical lines indicate stimulation. Intraperitoneal nembutal was used during preparation and observation.

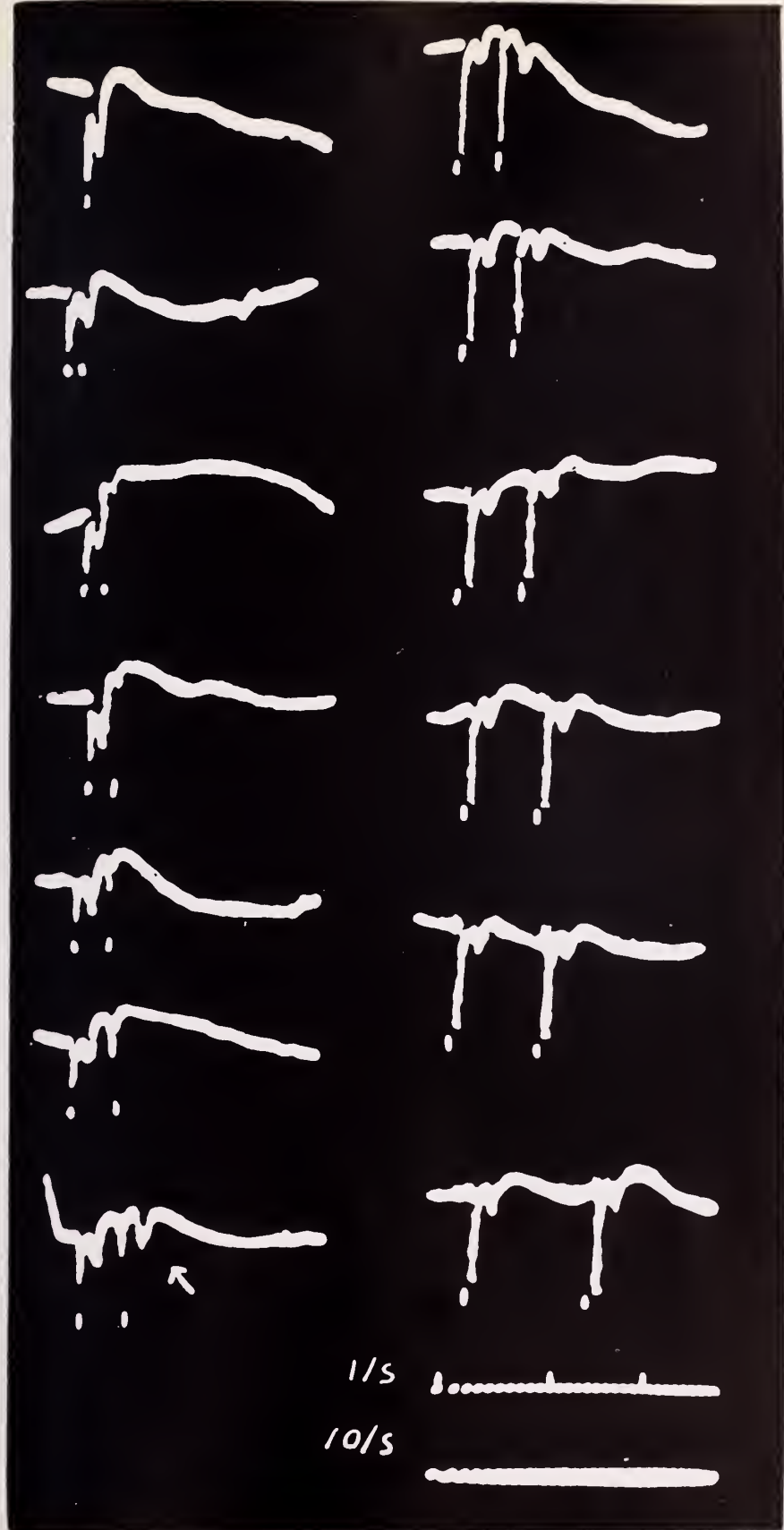


FIG. 8

### 3. *The Response to Two Successive Stimuli*

a) *Peripheral Stimulation.* A second stimulus was applied at successively greater intervals after a conditioning stimulus (Figure 6). As the interval was gradually increased, a second primary response first became evident during the secondary response to the conditioning stimulus. This first secondary and second primary seem to superimpose without influencing each other. As the interval between the two stimuli increases further, the second primary increases until it reaches the size of the first. Evidence of the second secondary response appears in distortion of the first secondary response in a direction determined by the phase interval. When, however, the second stimulus arrives sufficiently late so that the second secondary appeared after the completion of the initial wave of the first secondary, subsequent waves of the first secondary seem to be almost completely obliterated and the second secondary is completed (cf. Chang 1950). In general, the further apart the two stimuli, the closer the amplitude and duration of the second secondary to the amplitude and duration of the first. The mean time interval required for the second cortical response to match the first varies from preparation as mentioned above and is of the order of 0.3 to 0.5 seconds. It is interesting, however, that when the interval between the first and second stimuli is such that the first wave of the second secondary coincides with the second wave of the first secondary, a reinforcement appears. This effect has not been previously described, to my knowledge, but can be seen in Figure 8 of Chang's paper (12).

These observations are confirmed by the application of tetanic stimulation (Figure 7). When successive stimuli are applied during each preceding secondary, each succeeding secondary becomes smaller. When the interval between successive stimuli is adjusted so that the initial wave of a subsequent secondary response coincides with the second wave of the preceding secondary response, there is reinforcement as indicated above and the result is that a "driving" phenomenon appears, probably identical in nature with the photic and auditory driving described in electroencephalographic literature. As the frequency of stimulation increases, the secondary rapidly becomes small so that the response consists of a series of fairly uniform primaries interspersed among a low ripple of secondary response. Occasionally an alternation phenomenon appears, so that only each second stimulus results in a primary response. Accordingly, there is greater time for the development of secondaries as well. Otherwise, however, with increased frequency of stimulation, the primaries themselves decrease in amplitude. At this point there is no trace of the secondary. Finally, when the response consists of nothing but a fairly uniform series of small primaries, it becomes evident that all primaries after the first, which is, of course, of normal size, are superimposed upon a base line which follows the course of the secondary response to the first stimulus. With even greater frequency of stimulation, occasional primary responses drop out completely, at first irregularly then occasionally at regular intervals.

b) *Contralateral Cortical Stimulation.* As in the case of peripheral stimulation, with contralateral cortical stimulation as well, a second primary response first appears during the first secondary response (Figure 8). When the stimuli are

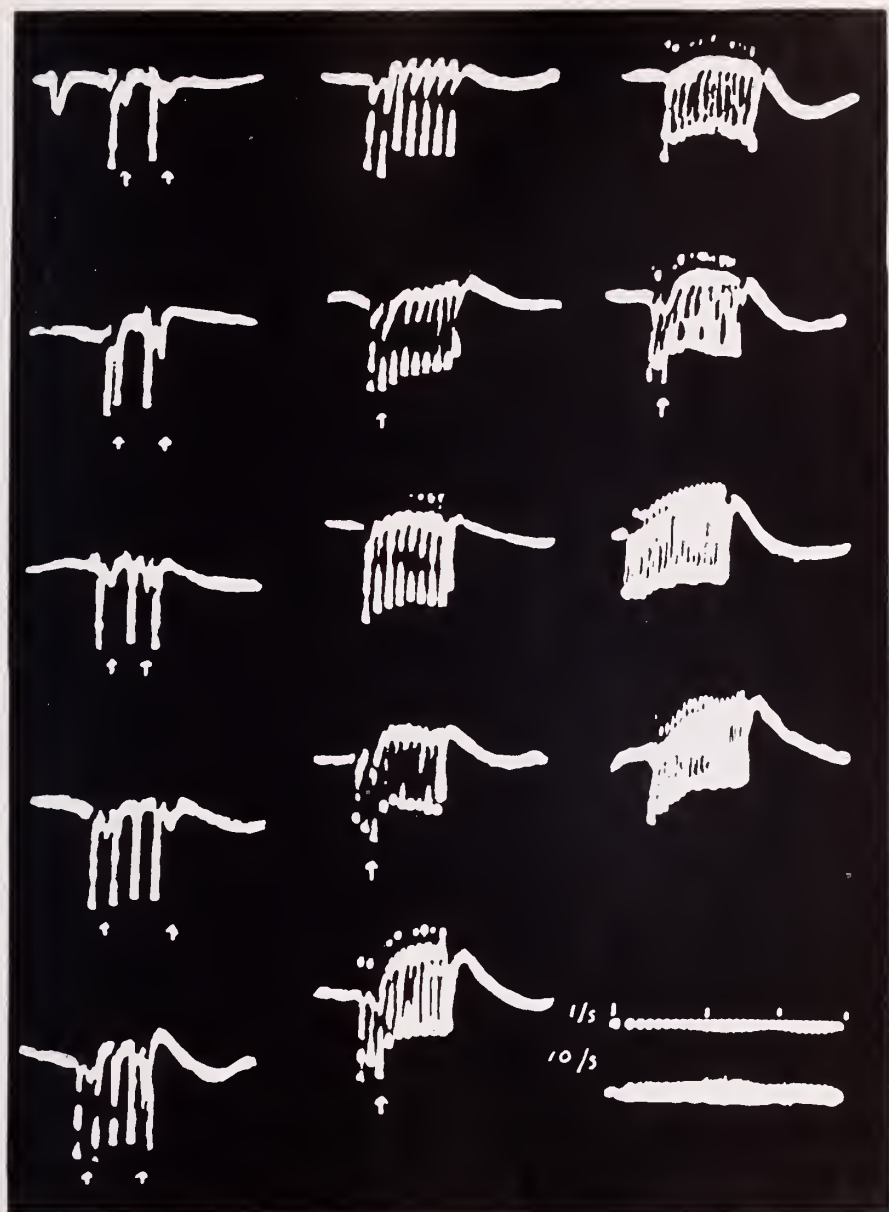


FIG. 9. With tetanic stimulation of the contralateral cortex a secondary response appeared after the first stimulus and unpredictably after one or more others. Arrows point to secondary responses. In this experiment intraperitoneal nembutal was used during preparation and during observation. This is the same experiment as that illustrated in figure 8.

arranged so that the second secondary begins during the early part of the first secondary, the first may be distorted by the second, in a manner determined by the phase interval. Usually a second stimulus appearing during the course of the initial wave of the first secondary response reinforces the response at that point.



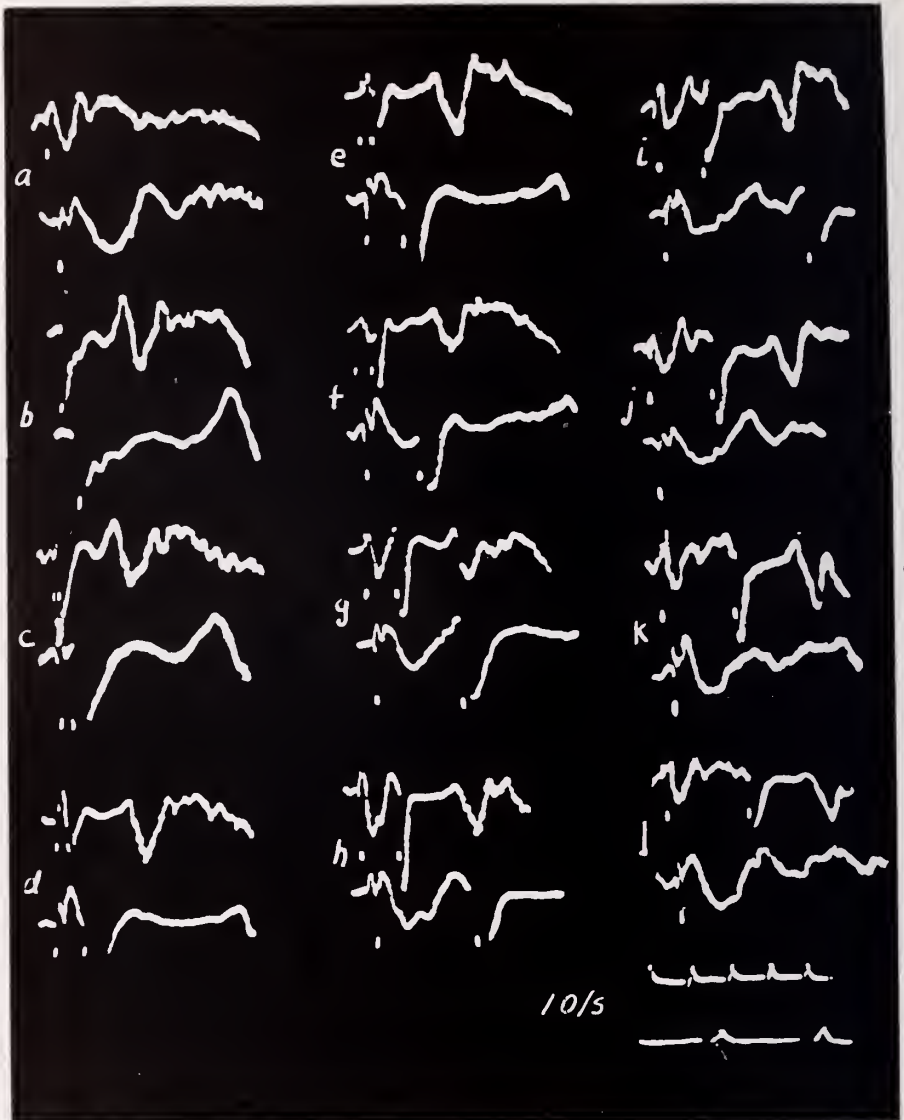


FIG. 10. When a stimulus was applied to the contralateral cortex at increasing intervals after stimulation of the proximal stump of the spinal cord the two responses were superimposed no matter what the interval but the response to contralateral cortical stimulation is much more prominent. The short vertical lines indicate the points of stimulation. Each response is indicated with slow sweep above and fast sweep below as shown by the time calibration. The first sample (a) illustrates the response to peripheral stimulation alone. The second sample (b) illustrates the response to simultaneous peripheral and contralateral cortical stimulation and in all subsequent samples the response to contralateral cortical stimulation follows the peripheral stimulation. In the last three samples (j, k, l) the contralateral cortical stimulus is delivered after the completion of the faster sweep (the lower trace). These observations are taken from the same experiment as that illustrated in figure 6.

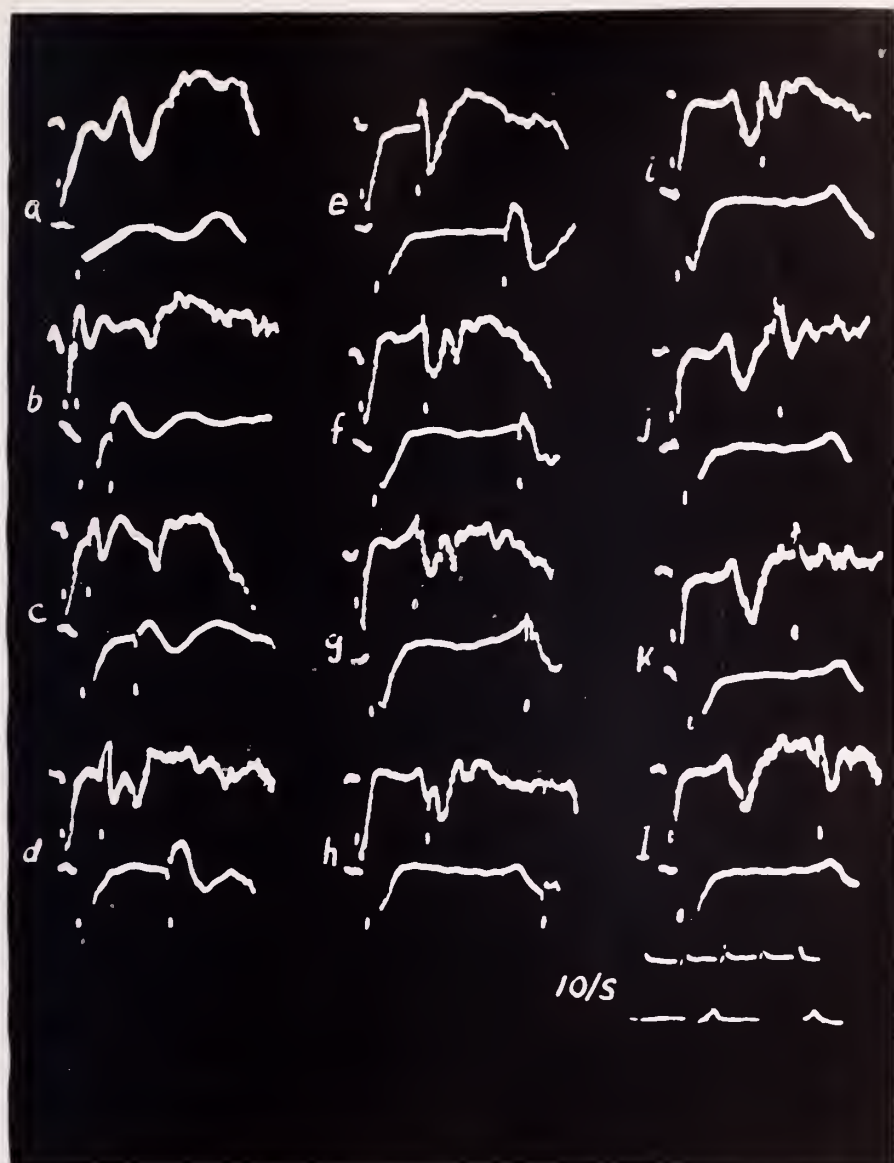


FIG. 11. When a stimulus is applied to the proximal stump of the spinal cord at varying intervals after the application of a stimulus to the contralateral cortex, the two cortical responses are superimposed but the response to contralateral stimulation is more prominent. Each sample is illustrated twice, with slow sweep above and fast sweep below as indicated by the time calibration. The short vertical lines indicate stimulation. In the first sample (a) both stimuli are delivered simultaneously. In all subsequent samples the peripheral stimulus follows the contralateral cortical stimulus. In the third column (i, j, k, l) the peripheral stimulus is delivered after the completion of the fast sweep. These observations are taken from the experiment which is also illustrated in figure 6.

However, a secondary response to the second stimulus fails to appear as a discrete wave until a minimal separation between the two stimuli is obtained, in these experiments of the order of 0.2–0.5 second. At that point a secondary response to the second stimulus appears rather abruptly. When the first wave of the second secondary coincides with the second wave of the first secondary there is considerable reinforcement not only of that wave, but also of the second wave of the second secondary. With tetanic stimulation of the contralateral cortex, the secondary response followed the initial stimulus and one or more other stimuli during the course of the tetanus (Figure 9). The more frequent the stimuli, the smaller the number of secondary responses observed so that at a given point a secondary response was observed only after the last stimulus of the series. For any given stimulus either the secondary response was there or it was not there, there was no partial response.

#### 4. *Combined Peripheral and Contralateral Cortical Stimulation*

When the first of the two stimuli is presented to the cord and the second to the contralateral cortex, the resultant pattern of secondary response can be seen to be determined by both individual responses superimposed one on the other (Figure 10). The pattern of response to contralateral cortical stimulation is always more distinct and more prominent than the pattern of response to stimulation of the cord.

When the initial stimulus is the contralateral cortical one and the second stimulus is the cord stimulus, again the resultant pattern may be seen to be composed of the two individual patterns and again the response to contralateral cortical stimulation is more prominent (Figure 11).

#### DISCUSSION

It is evident from the foregoing that one can record from the cerebral cortex of the anaesthetized cat or from the encephale isolé preparation when a homologous point on the contralateral cortex has been stimulated, a complex electrical response in which a primary and a secondary element can be recognized.

The corpus callosum secondary response resembles the afferent secondary response in the following respects: 1. It has similar latency and duration. 2. The corpus callosum secondary is just as variable in form and duration as compared with its primary as the afferent secondary is when compared with its respective primary. 3. If stimuli are delivered at proper intervals, a resonant reinforcement of a corpus callosum secondary can be obtained just as it can be obtained with the afferent secondary. 4. Neither the corpus callosum secondary nor the afferent secondary is modified by, or modifies the barbiturate bursts.

The corpus callosum secondary differs from the afferent secondary in the following respects: 1. With repetition of stimulation at frequencies of the order of several times a second, the corpus callosum secondary increases in amplitude while the afferent secondary becomes depressed. 2. When the interval between two successive contralateral cortical stimuli is just long enough to permit a second secondary response, this appears rather abruptly and in full amplitude.

Under similar circumstances the afferent secondary develops gradually. It is noteworthy too that the corpus callosum secondary and the afferent secondary do not interfere with each other but superimpose additively when stimuli are delivered to the contralateral cortex and the contralateral sensory pathway simultaneously or within a short time of each other.

What is the nature and significance of the secondary discharge in general? It seems reasonable to believe that the secondary discharge is an artifact of anaesthesia. It is clearly related to the depth of anaesthesia, becoming more distinct with increasing depth of anaesthesia to a certain point, after which it becomes less distinct (21, 24, 20). In nonanaesthetized or lightly anaesthetized animals, an afferent stimulus produces widespread bilateral prolonged alterations of the spontaneous rhythms. Similar observations were recorded previously (32, 9, 11, 20). Both Adrian (1, 2) and Forbes and Morison (21) suggested that anaesthesia simplified the operation of the cerebral cortex so that it functioned as a simple reflex mechanism acquiring a mode of function much simpler and different from its normal waking activity.

In this study no attempt was made to measure the depth of anaesthesia. The shift from nembutal anaesthesia to cerebral isolation was made in the course of this series of experiments to obtain a more constant and a smaller degree of cerebral depression. I doubt that any preparation was free of some degree of depression. There was no essential difference in the results obtained in the two types of preparation. However, in the "isolation" preparations there was considerably more spontaneous activity and the secondary responses were more prolonged and elaborate.

Lashley has recently said,

"It is now practically certain that all the cells of the cerebro-spinal axis are being continually bombarded by nerve impulses from various sources and are firing regularly probably even during sleep. The nervous activity which they in turn elicit depends upon the current physiological state of the neurones with which they are connected. It is probably not far from the truth to say that every nerve cell of the cerebral cortex is involved in thousands of different reactions. The cortex must be regarded as a great network of reverberatory circuits, constantly active. A new stimulus, reaching such a system, does not excite an isolated reflex path, but must produce widespread changes in the pattern of excitation throughout a whole system of already interacting neurones."

The relation between the reverberations of the normal waking cortex and its function have not yet been ascertained. Jarcho, Chang, and Gastaut and his coworkers have ascertained that thalamo-cortical reverberations influence the excitability of the cortex to subsequent afferent stimuli (24, 12, 22). Bishop suggested that such reverberations had a "sampling" function and McCulloch has suggested a scanning function (6, 29).

With increasing depth of anaesthesia spontaneous activity ceases rapidly. The tremendous difference between the duration of continuing electrical activity following a single stimulus in the unanaesthetized and the anaesthetized brain has been described by Burns (11). There seems to be a fairly broad interval in the development of narcosis with some anaesthetics during which spontaneous



activity is much diminished or absent, while the reverberating circuits stand ready for discharge so that a single afferent volley, which in the waking brain might have merely a timing effect, in the partially narcotized brain, will actually trigger in synchrony large groups of neurones to activity. However, the activity set off is rapidly damped and when enough responsive elements have recovered, another synchronous discharge can be set off. Critical stimulus repetition frequencies would be a function of such factors as number of elements ready to be triggered, frequency of reverberations, rapidity of recovery of reverberating elements. It is interesting that frequently repeating stimuli evoke a build up of the secondary discharge following contralateral cortical stimulation and also following local cortical stimulation with submaximal stimuli (1), whereas frequent stimulation results in depression of the secondary induced by afferent stimulation. Referring to the description of the narcotized brain as one in which large numbers of elements which in the waking state are continually active, remain inactive but ready to be discharged during narcosis, we may think of the difference between the two types of response in the following way. If an entire population of responsive elements is discharged by a first stimulus, a second can be effective only after the effects of the first have subsided almost completely. Such would be the case with afferent stimuli. If however, only a portion of the population is discharged by the first stimulus, the second stimulus would be more effective the sooner it is delivered, following the recovery from refractoriness of intermediate conducting elements because this second stimulus can evoke response in elements subliminally excited by the first stimulus. This would seem to describe the responses to contralateral cortical and to local cortical stimuli.

#### CONCLUSIONS

1. The electrical response of the cerebral cortex of the anaesthetized cat to contralateral cortical stimulation consists of two elements the first of which resembles the primary response to afferent stimuli in its time relations and constancy and the second of which resembles the secondary discharge evoked by afferent stimuli.

2. While repeated stimulation depresses the secondary response to afferent stimuli, the secondary discharge in response to contralateral cortical stimuli is increased.

3. When peripheral stimuli are provided at proper intervals, a resonant reinforcement of the secondary discharge can be obtained suggesting the "driving" phenomenon. Such a resonant reinforcement of the secondary discharge can be evoked by contralateral cortical stimuli as well.

4. It is suggested that the secondary discharge is an artifact of anaesthesia evoked by any stimulus arriving at the cortex. In addition to giving its electrical sign of arrival at the cortex, the stimulus, under proper conditions of narcosis triggers elements of reverberating circuits which are inactive but available to discharge. During narcosis, therefore, stimuli have an activating and synchronizing effect on responsive reverberating circuits, while presumably in the non-

narcotized brain, stimuli act essentially by modifying the timing of the reverberations.

### *Acknowledgment*

*The author would like to acknowledge with gratitude the direction and supervision of Professor Harry Grundfest in this project.*

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## HIGH ALKALI-RESISTANT HEMOGLOBIN IN SIBLINGS WITH UNUSUAL BLOOD PICTURES\*

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The amount of hemoglobin remaining after exposure of red blood cells to sodium hydroxide for one minute has been termed by Singer (1) the alkali-resistant hemoglobin. It is a measure of the "fetal" hemoglobin which normally is absent, or almost so, after the age of one year (2). Although Singer found that there may be slight increases in some patients exhibiting a variety of miscellaneous conditions, the most common disorders characterized by an appreciable elevation of alkali-resistant hemoglobin are sickle cell anemia and the Mediterranean syndromes. This paper will present two cases with elevated alkali-resistant hemoglobin in siblings, each of whom has an apparently different hematologic disorder from the other, and neither of which appears to be sickle cell anemia or Mediterranean disease.

## CASE REPORTS

*Case 1.* J. R. (MSH #19698) is a seven year old Caucasian girl of Anglo-Saxon stock who was hospitalized on December 13, 1953 with a chief complaint of pallor and easy fatigability of two months duration.

Past history: The child was the product of a normal pregnancy and uneventful delivery. The parents and two siblings have been in good health. Growth and development were normal. The child received routine immunizations and had chicken pox and measles without complications. No allergic history could be elicited.

Present illness: The patient had been in good health until two months prior to admission when pallor and easy fatigability were noted by her mother. The child was found to be anemic by the family physician who hospitalized her in their upstate New York community. She was then transferred to The Mount Sinai Hospital.

There was no history of contact with chloramphenicol or other drugs or toxins. Several aspirin tablets were taken during the months prior to hospitalization. A fly spray, plant spray and DDT were used about the home, but the child had no excessive contact with them. There have been no skin lesions or joint pains and the system review was entirely negative.

Physical examination revealed a well developed, fair, somewhat pale white female of seven years of age who was in no distress and appeared neither acutely nor chronically ill. The blood pressure was 85/50 mm. Hg and the pulse, 120 per minute. The temperature was 99.0°F. The respirations were 20 per minute. There was no icterus and no skin lesions were present. The conjunctivae were pale and the sclerae were not icteric. Fundoscopy revealed pallor, but no hemorrhages or exudates. ENT examination was negative except for occasional petechiae on the buccal mucosa. Some very small non-tender nodes were present in the cervical, axillary and inguinal regions. The chest was symmetrical and clear to percussion and auscultation. The heart was not enlarged. There was a grade II systolic murmur heard best in the third interspace to the left of the sternum and not transmitted. There was no thrill, rub or diastolic murmur. The abdomen was soft and non-tender with no palpable

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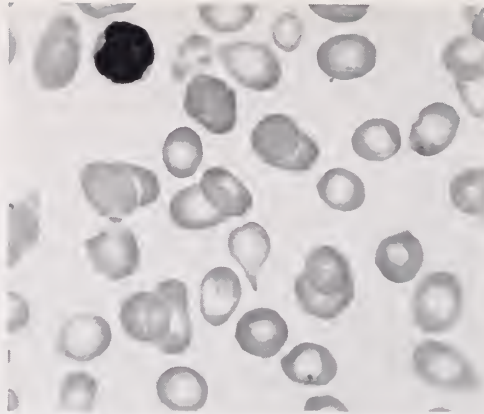


FIG. 1. J. R. ( $\times 950$ ) Blood smear showing hypochromia, and moderate anisocytosis and poikilocytosis of the red cells.

organs or masses present. Neurological examination and examination of the extremities and joints were negative.

Laboratory studies: The hemoglobin was 6.5 grams per cent; red cell count, 2.5 million per cu. mm.; hematocrit, 22 per cent. The red cell indices were MCV 88, MCH 26, MCHC 30. The erythrocytes (Fig. 1) exhibited slight hypochromia, and moderate anisocytosis and poikilocytosis. The white cell count was 2700 per cu. mm. with 14% neutrophils, 2% bands, 83% lymphocytes and 1% monocytes. The platelet count was 42,000 per cu. mm. 2.6% reticulocytes were present. The bone marrow aspirate was hypocellular with very rare megakaryocytes and scattered clusters of normoblasts. Most of the remaining cells were lymphocytes (27%), plasma cells (9%) and reticulum cells (7%), a reflection of the general hypoeellularity. The M:E ratio was 1:1. The bleeding time was  $17\frac{1}{2}$  minutes. The tourniquet test was positive. The serum prothrombin activity was 15 seconds. There was no clot retraction in one hour. Other coagulation studies were normal.

The fecal urobilinogen excretion was 10 mg. per 24 hours. The hemolytic index was 6. The urine urobilinogen excretion was less than 1 mg. per 24 hours. There were no methemalbumen or other abnormal pigments in the plasma. Several "L. E." preparations were negative. Smears made from the buffy coat of the peripheral blood did not reveal any immature cells. The blood urea nitrogen was 18 mg. per cent. The total protein was 7.1 grams per cent with 4.7 grams of albumen and 2.4 grams of globulin. The cephalin flocculation test was negative. The urinalysis was normal and the stool was guaiac negative.

Osmotic fragility studies revealed a faint trace of hemolysis at .52 per cent NaCl, and complete hemolysis at .32 per cent NaCl. (The control specimen showed beginning hemolysis at .48 per cent NaCl, with complete hemolysis at .28 per cent NaCl.) The mechanical fragility was 3.0 per cent with a control of 4.0 per cent. Repeated determinations were similar, but in some hemolysis began at .48 per cent NaCl. The incubated osmotic fragility specimen showed beginning hemolysis at .68 per cent NaCl and complete hemolysis at .44 per cent NaCl. (The control specimen showed beginning hemolysis at .64 per cent NaCl and was complete at .44 per cent NaCl.) The incubated mechanical fragility value was 16 per cent with a control of 12 per cent.

The serum iron level was 103 gamma per cent. The total iron-binding capacity was 373 gamma per cent. The total bilirubin was 0.6 mg. per cent. The alkali-resistant hemoglobin was 20.8 per cent. Repeat determinations were 19.9 per cent, 19.5 per cent and 20.6 per cent. Paper electrophoretic studies of the patient's hemoglobin were normal. A sickle cell preparation using sodium metabisulfite was negative. Antibody studies, including the direct and indirect Coombs tests, the autohemolysin test, the acid hemolysin test, and studies of serum

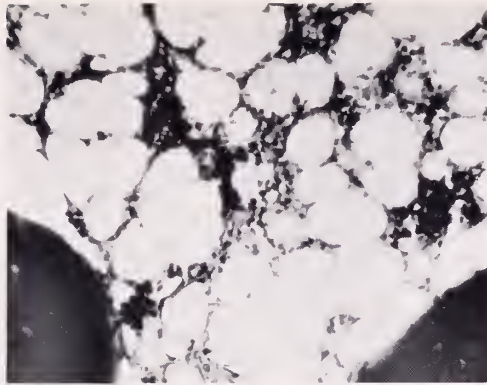


FIG. 2. J. R. ( $\times 100$ ) Bone marrow biopsy. Fatty marrow with patchy distribution of hematic cells.

antibodies at various temperatures, using red cells suspended in saline and trypsinized red cells, were negative.

A surgical biopsy (Fig. 2) of the sternal marrow was obtained which revealed much fatty tissue with a patchy distribution of cellular elements, many of which were clusters of normoblasts. An X-ray bone survey was negative.

The patient was clinically comfortable during the entire hospitalization. She was afebrile except for one day when a thrombophlebitis of the left arm developed following the transfusion of 500 cc. of whole blood.

Radioactive iron turnover studies revealed a half-time of disappearance from the plasma of 119 minutes, the normal ranging from 70–120 minutes in an adult. This value is probably abnormally prolonged for a child.

A diagnosis of hypoplasia of the bone marrow, etiology unknown, was made. The patient was discharged from the hospital and has been seen periodically since then.

The patient's parents and two siblings were studied to see whether the elevation of alkali-resistant hemoglobin might be a familial occurrence. The alkali-resistant hemoglobin values and blood counts of the entire family are listed in Table I. The patient's sister, M. R., has a definite elevation of alkali-resistant hemoglobin. The blood counts and blood smears of the family revealed no abnormality other than a reticulocytosis of 10.8 per cent in M. R., whose hemoglobin was 12.8 grams per cent and whose blood smear showed polychromatophilia and the presence of many spherocytes. Further workup of M. R. was therefore undertaken.

TABLE I

*Alkali-resistant hemoglobin values and blood counts of the R. family. Normal alkali-resistant hemoglobin level is 0–1.7%. Values between 1.7 and 2.0% are not significantly elevated*

	Alkali-Resistant Hgb	Hgb	Hct	RBC $\times 10^6$	Ret	WBC $\times 10^3$	Pt	Poly/Lym
	%	gm%	%		%			
J. R.	19.5	6.5	22	2.5	2.4	2.1	R	27/71
Mrs. R.	1.8	14.0	44	4.7	0.8	8.3	N	61/38
Mr. R.	1.6	15.3	50	5.3	0.8	7.0	N	67/30
T. R.	1.8	14.0	41	4.5	0.8	8.7	N	68/28
M. R.	4.4	12.8	35	3.9	10.8	8.4	N	55/38

R—Reduced. N—Normal.

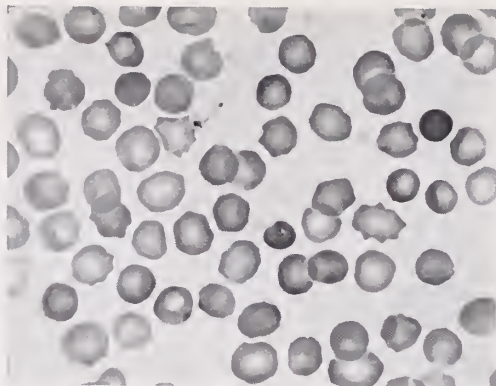


FIG. 3. M. R. ( $\times 950$ ) Blood smear showing spherocytes

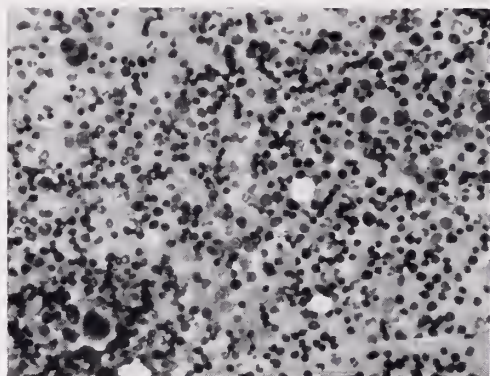


FIG. 4. M. R. ( $\times 100$ ) Aspirate of bone marrow showing marked hypercellularity and erythroid hyperplasia.

*Case 2.* M. R. is an eleven year old girl, the product of a normal pregnancy and labor. Growth and development have been normal. There was a past history of measles and chicken pox. The history of exposure to drugs or possible toxins was similar to that of her sister, J. R. System review was negative. There was no past history of pallor or icterus. Physical examination revealed a well developed, well nourished young girl in no distress who appeared neither acutely nor chronically ill. Physical findings were entirely normal. There was no icterus, adenopathy or hepatosplenomegaly. There was no bile in the urine.

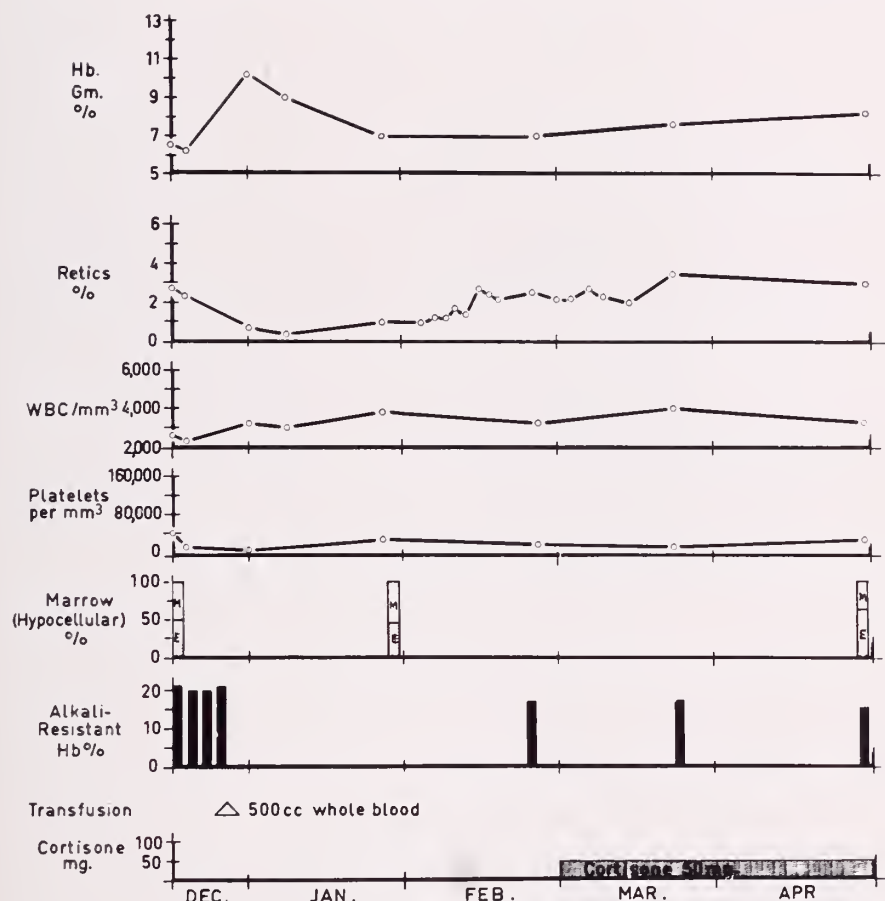
The blood smear (Fig. 3) showed the presence of many spherocytes and polychromatophilic cells. The hemoglobin was 12.8 grams per cent; the hematocrit, 35 per cent; the red cell count, 3.9 million per cu. mm. The red cell indices were MCV 90, MCH 35, MCHC 36. The white cell count was 8400 per cu. mm. with 50% neutrophils, 5% bands, 3% eosinophiles, 38% lymphocytes and 4% monocytes. The platelet count was 220,000 per cu. mm. and 10.8 per cent reticulocytes were present. The bone marrow aspirate was extremely hypercellular with marked erythroid hyperplasia (Fig. 4). The fecal urobilinogen excretion was 280 mg. per 24 hours; the hemolytic index being 72. As can be seen in Table III, there was markedly increased osmotic and mechanical fragility of the erythrocytes demonstrable both in fresh and incubated blood specimens. Antibody studies, including the direct and indirect Coombs' tests, the acid hemolysin test, and studies of the serum at various temperatures, employing cells in saline and trypsinized red cells, were negative. However, the autohemolysin test of Dacie was positive at 24 hours. Spectroscopic studies

TABLE II  
M. R. Blood values and myeloid:erythroid ratios

Date	Hgb	Hct	RBC $\times 10^6$	Ret	Plat. $\times 10^3$	WBC $\times 10^3$	Poly/Lym	M:E
	gm%	%		%				
12/53	12.8	35	3.9	10.8	240	8.4	55/38	1:1
2/54	13.3	37	4.2	8.0	250	9.0	62/34	1.2:1
4/54	12.6	35	4.2	10.0	228	10.2	76/20	1:1

of the plasma did not reveal the presence of methemalbumin or any other abnormal pigments. The serum iron level was 215 gamma per cent and the total iron-binding capacity was 408 gamma per cent. The total serum bilirubin level was 1.6 mg. per cent. It is felt that M. R. has a well-compensated spherocytic hemolytic process.

Studies of M. R. over the next four months (Table II) reveal a continued reticulocytosis,



J.R. ♀7

FIG. 5. J. R. Blood values, myeloid:erythroid ratios, alkali-resistant hemoglobin levels and therapy.



TABLE III

*Red cell fragility values of the R. family. All are essentially normal except for M. R. who has a marked elevation of mechanical and osmotic fragility values in both fresh and incubated specimens*

	Osmotic Fragility*	Mechanical Fragility	Incubated Osmotic Fragility*	Incubated Mechanical Fragility
	% NaCl	%	% NaCl	%
J. R.	.52-.36	3.0	.68-.48	16.0
Mr. R.	.44-.36	4.1	.64-.52	18.2
Mrs. R.	.44-.28	3.6	.64-.44	15.1
T. R.	.40-.32	3.1	.60-.44	16.4
M. R.	.60-.32	17.0	.80-.48	62.0
Control	.48-.32	4.0	.64-.48	12.0

\* The figures are the zones of partial hemolysis.

spherocytosis, erythroid hyperplasia of the bone marrow and elevation of alkali-resistant hemoglobin of 4-5 per cent. She continues to appear perfectly well and is entirely asymptomatic.

J. R. (Fig. 5), since being discharged from the hospital, has continued to have a pancytopenia, 1-4 per cent reticulocytes, hypocellular bone marrow aspirations with relative erythroid hyperplasia and 17-20 per cent alkali-resistant hemoglobin levels. She has been placed on Cortisone 50 mg. daily with resultant marked rounding of the face and a slight rise in hemoglobin, but no other significant change in her laboratory findings.

Laboratory investigations of the father, mother, and fourteen year old brother revealed that all had normal blood values (Table I) and normal bilirubin levels (between 0.4 and 0.8 mg. per cent). Osmotic and mechanical fragility determinations on fresh and incubated blood samples were similar to the control specimens (Table III).

#### DISCUSSION

Except in infancy, an alkali-resistant hemoglobin value of about 20 per cent has, heretofore, been reported only in certain well-recognized hemolytic syndromes characterized by intrinsic erythrocyte abnormalities, e.g. Mediterranean disease or sickle cell anemia (2). In contrast to the active bone marrow characterizing these latter conditions, patient J. R. exhibited bone marrow hypoplasia reflected by a peripheral pancytopenia and a probably delayed disappearance of  $\text{Fe}^{59}$  from her plasma. It was not feasible to do a red cell survival in this seven year old child. However, the low hemolytic index and normal serum iron levels mitigated against a hemolytic process in this patient. Nevertheless, it must be observed that following her transfusion, her hemoglobin remained elevated for only about five weeks, and she has persistently had a slight reticulocytosis with no apparent elevation of hemoglobin. Therefore, the possibility of a low-grade hemolytic process cannot be entirely excluded.

Due to the familial incidence of the above-mentioned conditions characterized by an elevation of the alkali-resistant hemoglobin, the other members of J. R.'s family were studied, revealing no marked abnormality in any member, except a sister, M. R. who had a moderate elevation of alkali-resistant hemoglobin of 4-5 per cent. Further investigation of M. R. demonstrated the presence of a well-compensated spherocytic hemolytic process with no evidence of an autoimmune mechanism.

The possibility that M. R. had hereditary spherocytosis was entertained. Investigation of the parents revealed a lack of spherocytes and normal osmotic and mechanical fragilities of both fresh and incubated blood samples. This lack of spherocytes and abnormal fragilities in the parents, according to Young (3), does not completely rule out hereditary spherocytosis, as the parents of 3 of 29 cases of that disease did not demonstrate hematologic abnormalities, although the cases had findings typical of hereditary spherocytosis. There is no reason to suspect illegitimacy in the cases presented in this paper. Young explains this phenomenon as due perhaps to "a low degree of penetrance or expression" or a gene mutation in some cases.

It is tempting to try to link the hematologic abnormalities exhibited by the two sisters, both of whom have an elevation of alkali-resistant hemoglobin, although quite different in amount. If it be postulated that M. R. has hereditary spherocytosis, then it is tempting to speculate that J. R.'s hypoplasia represents a "hypoplastic crisis" described in that disorder by Owren (4) and Dameshek and Bloom (5). However, against that is the duration of the hypoplasia which has been present for five months, with a great likelihood of it having existed at least two months prior to that, the lack of spherocytes, the essentially normal incubated osmotic and mechanical fragilities, and the lack of an elevated stool urobilinogen, although Owren (4) states the latter is decreased during a crisis. The high level of alkali-resistant hemoglobin (20 per cent) is much higher than the approximately 4-5 per cent values found in three out of eight cases of congenital hemolytic anemia reported by Singer (1), and the 2-4 per cent values found in five of nine cases reported by Chernoff (6). Therefore, there is no evidence that J. R. is an example of hereditary spherocytosis, although her sister, M. R., has a spherocytic hemolytic process.

The possibility of a Mediterranean trait or anemia must be considered in view of the elevated alkali-resistant hemoglobin. However, the Anglo-Saxon ancestry, and lack of splenomegaly and normoblastosis in the peripheral blood of both siblings is against the more full-blown forms of Mediterranean disease. In addition, it is not generally believed that "aplastic crises" occur in Mediterranean disease. The normal serum iron level in J. R., and the presence of spherocytosis in M. R. likewise mitigate against that diagnosis.

The Caucasian background, and particularly the normal paper electrophoresis patterns and lack of sickling rule out sickle cell anemia.

There was a lack of congenital anomalies and other stigmata of the Fanconi syndrome. There was no clinical or laboratory evidence for paroxysmal nocturnal hemoglobinuria.

#### CONCLUSION

Apparently the only definite common defect exhibited by the two siblings is that of an elevation of alkali-resistant hemoglobin of 17-20 per cent and 4-5 per cent respectively. The values in the other members of the family are within normal limits in the case of the father (1.6 per cent), and within one standard deviation of normal in the case of the mother (1.8 per cent) and the brother (1.8 per cent). The significance and interpretation of these borderline values,

which are reproducible, is probably open to question at this stage of our knowledge. Of the three siblings in the family, one (male) shows no definite hematologic abnormality, the second (female) has a very cellular bone marrow with a well-compensated, active, spherocytic hemolytic process, and the third (female) exhibits bone marrow hypoplasia with the possibility of a low-grade hemolytic process. Attempts at explaining the hematologic findings evident in the two sisters on the basis of a common well-recognized syndrome such as hereditary spherocytosis or Mediterranean disease is difficult, and of sickle cell anemia and several other conditions is untenable. It is possible that both sisters were exposed to an unknown agent which caused marrow hypoplasia in one and a spherocytic hemolytic process in the other, or one abnormality may be a stage in the development of the other. Perhaps the passage of time will elucidate the relationship, if any, between the disorders present in both siblings.

The failure to find a satisfactory common denominator to the dyscrasias affecting the siblings has resulted in a fruitless search for a definitive explanation of the high alkali-resistant hemoglobin levels. However, it is possible that in these cases revival of alkali-resistant hemoglobin production may in some fashion be a compensatory phenomenon due to the marrows of these children being subjected to the severe chronic stress (1) imposed by their basic hematologic disorder.

#### SUMMARY

A case of bone marrow hypoplasia accompanied by a high alkali-resistant hemoglobin in a seven year old girl was presented.

Investigation of the family revealed normal parents, an older female sibling having a well-compensated spherocytic hemolytic process with moderate elevation of alkali-resistant hemoglobin, and an apparently normal male sibling.

Attempts at correlating the clinical and laboratory findings of the siblings as different manifestations of some well-known clinical entity have been unsatisfactory.

There is no evidence that these cases are examples of an inherited elevation of alkali-resistant hemoglobin.

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## OCULAR ECZEMA: ITS CLASSIFICATION AND TREATMENT\*

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As a result of the emphasis that has been placed on contact allergy as the cause of eczematous dermatitis, physicians are apt to overlook the fact that other types of eczematoid dermatitis, often very similar in appearance, do occur and must be differentiated if therapy is to be successful. In fact, in certain locations such as the eyelids, eczema, particularly of the chronic type, appears, more often than not, to be due to causes other than contact allergy. The major types of eyelid eczema encountered are: allergic eczematous dermatitis, secondary to contact allergy; staphylococcal eczema, secondary to infection of the lid margins with pathogenic staphylococci; and, certain generalized dermatoses such as atopic dermatitis, neurodermatitis, seborrheic dermatitis, and psoriasis. In each instance the treatment is entirely different and incorrect therapy based on the wrong diagnosis not only will yield no benefit, but, at times, may result in serious aggravation of the original dermatitis.

The term eczema is used herein to describe any skin reactions situated principally in the epidermis, characterized grossly by some of the following: erythema, papulation, fasciculation, oozing, crusting, scaling, thickening, pigmentation and itching, regardless of the cause or the mechanism of production (1). The skin of the eyelids appears to be particularly susceptible to inflammation for several special reasons. First, its fine texture and extreme thinness permits easy traumatization and the penetration of all types of noxious substances. Second, the eyelids are especially exposed to physical trauma (rubbing, heat, sun, wind, and ocular secretions) as well as to various drugs and chemicals applied elsewhere about the head and face. Thus, although a facial cream or hair tonic is not directly applied to the eyelids, the eyelids may eventually prove to be the only site of the eczema, as even a minimal amount of the irritant indirectly contacted by means of a pillowcase during sleep or the fingers, is able here to penetrate sufficiently to cause the reaction, in contrast to its inability to penetrate the thicker and stronger skin where it was originally applied more generously. Similarly, the skin of the eyelids because of its delicacy and its vulnerable position may react to bacterial products or ocular medicaments that occur in tears, which would be harmless elsewhere on the skin. This special susceptibility of the eyelid skin holds both for primary irritants and true sensitizers (allergens).

### ALLERGIC ECZEMATOUS DERMATITIS

The most common cause of acute eczema of the eyelids is contact allergy. This usually follows the use of cosmetics or ophthalmic drugs but may, on occasion result from contact with articles of apparel, jewelry, metals, plastics, other chemicals and numerous animal or vegetable products. The dermatitis, which may be

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either unilateral or bilateral, occurs mostly in women, probably more because they use cosmetics so universally than because of any endocrine factor. There need be no previous history of familial or personal allergy. The diagnosis is based on a careful history, positive patch test, and the ruling out of other major causes of eyelid eczema, namely primary ocular infection or generalized dermatoses. In addition, one must be certain that the contact dermatitis present is due to allergy rather than to primary irritation. The highlight of therapy is to eliminate the sensitizing agent; the use of any other allergenic substance may aggravate the condition seriously.

The mechanism for the production of contact allergy has been fairly well established. It is basically a "delayed" type of allergic response. Reactions, once hypersensitivity has been established, do not usually occur until twenty-four to forty-eight hours after antigen contact. As distinguished from the "immediate" (atopic) type of allergy, there appear to be no circulating antibodies and in general passive transfer of the allergy does not occur. While the non-protein substances causing the allergy are themselves not primarily antigens, it is believed that they form true antigens in the body by union with the host's tissues. These relatively simple chemicals, known as haptens, combine with body proteins forming conjugates that act as antigens. The haptens confer specificity on the conjugate; hence the allergy is directed against the hapten and not against the protein (2). Thus, the substitution of a drug that is chemically similar to one that previously caused sensitivity in a patient is dangerous.

The site of eczematous (contact-type) allergic dermatitis appears to be strictly epidermal, not deeper in the skin. For this reason, in order to prove contact allergy

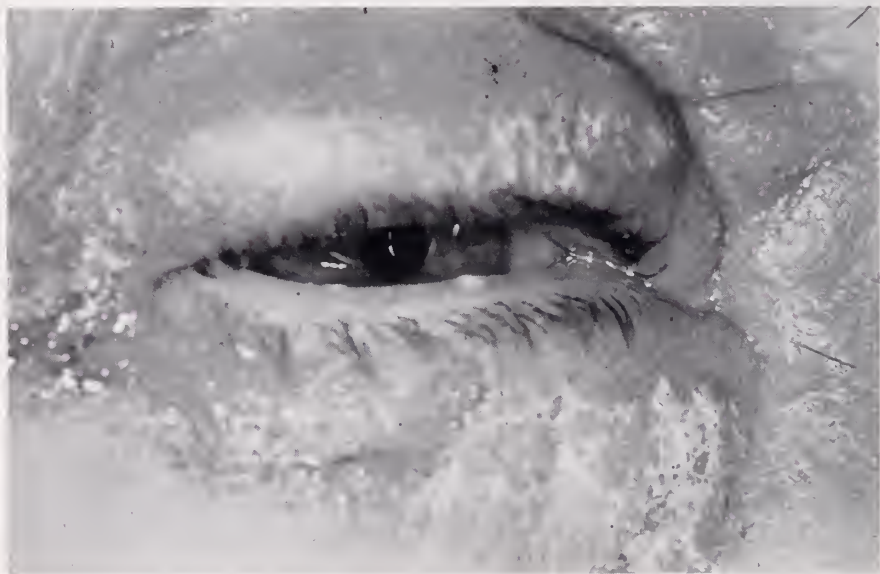


FIG. 1. Allergic dermatoconjunctivitis due to eserine eye-drops. Intolerance to eserine is rarely allergic; usually an irritative follicular conjunctivitis, without eczema, occurs.

patch tests are necessary. Immediate wheal testing by intradermal injections is not a correct diagnostic procedure here, because even the most superficial intracutaneous or scratch test carries the allergen through the epidermis into the cutis (3).

It appears that the eczematous allergic reaction is not a stationary condition (4). Sensitive donor skin soon loses its sensitivity when transplanted to a normal recipient. Normal skin, on the other hand, when transplanted to a sensitive host acquires the latter's sensitivity within a few days. This would imply that the factor responsible for eczematous allergy comes from within the body. There is evidence, moreover, that in some manner it is related to the lymphocytes.

*Eczema of the Eyelids Due to Ophthalmic Drugs:* Allergy to ophthalmic drugs is a common occurrence and may cause exceedingly serious reactions. Since the conjunctiva is usually the focal point of contact, the allergic reaction generally begins as a conjunctivitis, soon spreading to the adjacent skin as a typical allergic dermatitis (5). The characteristics of this classical form of inflammation, in the order of their appearance are: itching of the eyes; papillary conjunctivitis; eczema of the skin of the eyelids; and, conjunctival eosinophilia. The earliest signs of eczema due to eye drops may be at the canthi and lower lids; with ointments, the lid margin is first involved. Although any ophthalmic drug may cause allergy in susceptible individuals, allergic dermatitis is usually encountered following the use of anesthetics, antibiotics, sulfonamides, mydriatic alkaloids, and mercurials (Figs. 1, 2). Even if the active ingredient in an ophthalmic preparation is guiltless, allergy may result from the ophthalmic vehicle used, especially



FIG. 2. Allergic dermatitis conjunctivitis due to bacitracin ointment

ointment bases and preservatives in the vehicle. Now that it is required by law that commercial ophthalmic solutions be prepared sterile and contain suitable preservatives (6-9) such allergy is assuming greater importance.

Drug intolerance sometimes may be the result of drug irritation rather than drug allergy. Ocular irritation is differentiated from allergy in that a non-specific inflammation, often follicular, results without the occurrence of eczema or eosinophilia. This usually is due to the prolonged use of the miotic alkaloids and related synthetic products such as eserine, pilocarpine, neostigmine, mecholyl and diisopropylfluorophosphate, all of which are prone to deteriorate forming irritating end products (10). Such drug irritation can be avoided by using properly prepared solutions of the same drug, while drug allergy requires substitution of a different drug. It is therefore of great importance to make the distinction between these two types of drug intolerance.

Eyelid eczema may also occur following the systemic use of drugs. On occasion such reactions may recur at fixed sites only (fixed drug eruption). Phenolphthalein, barbiturates, antipyretics, quinine, iodides, and bromides are especially prone to cause such reactions. Here patch tests are of little value although there may be marked clinical sensitivity when the drug is ingested.

*Eczema of the Eyelids Due to Cosmetics:* Cosmetics have been widely used for thousands of years, despite sporadic, unsuccessful attempts to outlaw the custom, such as the introduction of a bill in the British Parliament in the Eighteenth Century proposing to make the beguiling of men into matrimony by their use punishable as for witchcraft. So much is now known about the action of cosmetics on the skin and the exclusion of harmful ingredients is so regulated by law that the good accomplished by their use far outweighs the occasional harm that occurs (11). Actually, if we consider how universally cosmetics are used the percentage incidence of allergies to them is extremely low.

Unlike drug allergy, cosmetic allergy usually begins by involvement of the upper lid especially at the medial portion. Generally the conjunctiva is uninfamed and without eosinophilia. In the diagnosis of eyelid eczema due to cosmetics it must be remembered that only the eyelids may react even if the allergenic substance was applied at a place remote to them. Careful history taking is essential; the use of leading questions often is important in opening avenues of thought otherwise dismissed by the patient as immaterial. Just because a cosmetic has been used previously without reaction for a long period of time, it should not be completely exonerated because the manufacturer only now may have changed the formula, or the method of production, in some way. In diagnostic testing for cosmetic sensitivity it is better to apply the cosmetic in the way it is generally used instead of doing a patch test, because in normal use the uncovered cosmetic loses most of its substance by evaporation (12). Covering the cosmetic by a patch does not permit this evaporation and may give rise to false positive reactions with cosmetics that are actually harmless when used in the ordinary manner.

Nowadays most allergies to cosmetics are due to the perfumes used and to impurities in manufacture as the hitherto most flagrant offenders have been eliminated. Sometimes, while the cosmetic itself is innocent, contamination of the con-

tainers may cause allergies. Allergies to a few important types of cosmetics are noted below:

*Nail Polish and Nail Lacquer:* Of all ocular allergies traced to cosmetics, those due to nail polish and nail lacquer are by far the most common. Dermatitis involved the eyelids in 78 of 100 cases of all types of nail polish sensitivity in one reported series (13). The offending ingredients are believed to be the synthetic resins such as methacrylates.

*Face Powders:* Face powders used to be sensitizers because of the orris root and the rice powder content. These ingredients are rarely used at present, having been replaced by titanium salts. Now any allergy to it is usually traced to perfumes, and to impurities in manufacture and packaging.

*Facial Creams:* Facial creams such as plain cold cream and vanishing creams are not often sensitizers. In both, the major offender is either lanolin, or cocoa butter and almond oil.

*Lipstick:* Lipstick dermatitis is usually due to the indelible dyes used.

*Hair Preparations:* Hair dyes and rinses contain both sensitizers and toxic products. The most commonly used ingredient, paraphenylenediamine, may be both toxic and allergenic. Generally, allergies occur from its use, but in susceptible persons serious toxic reactions may develop, sometimes terminating fatally. Paraphenylenediamine is also the major sensitizer in allergy to furs.

*Eyelash Dyes and Mascara:* Eyelash dyes, other than those of vegetable origin are prohibited by public health authorities because of their paraphenylenediamine content. Allergies are infrequent. Allergy to mascara, when it occurs, is due to the base used, as the dyes employed, such as carbon black and methylene blue, are rarely sensitizers.

*Treatment of Eczema of the Eyelids Due to Contact Allergy:* The basic principles in the treatment of contact allergy are the elimination of the offending substance if it has been identified, or of all possible offenders if no definite cause has been established, and the avoidance of any new medicament that may aggravate the condition. Rather than incite an already hyperergic skin, which now may react allergically to medicaments it can tolerate at other times, it is preferable to use little or no local therapy. The safest procedure is the systemic use of steroids such as corticotropin, cortisone, or hydrocortisone which are very valuable in severe reactions. Since they need only be given for several days they are thus rarely contraindicated. The local use of hydrocortisone or cortisone is often effective, but it should be emphasized that sometimes allergies to even these preparations may occur. Antihistaminics in any form do not appear to be effective in contact allergy. When drug allergy occurs, it is sometimes necessary to continue the use of another drug having a similar pharmacologic action. The drug chosen for this purpose should differ as much as possible in its chemical structure from the original excitant. Should no drug be available for substitution in the place of the original offender, and it must be used the concomitant systemic administration of sufficiently large amounts of steroids, preferably ACTH, is advised. Generally the local use of these steroids will not suffice to prevent the allergic reactions.



Hypoallergic cosmetic preparations are now available for those persons suffering from allergies to cosmetics. Even if these should prove to be sensitizers, special formulae may be obtained for such individuals from the manufacturers.

#### STAPHYLOCOCCAL ECZEMA OF THE EYELIDS

The importance of staphylococcal infections of the lid margin and conjunctiva as a major cause of eczema of the eyelids has not received the emphasis it deserves. While dermatitis actually is a relatively infrequent complication of such common infections, recent experience indicates that the condition is the most frequent cause of chronic eyelid eczema encountered, yet because its importance is not generally appreciated it is often overlooked.

The simpler term "staphylococcal eczema" (14) is preferable to the rather redundant and awkward "infectious eczematoid staphylococcal dermatitis" which has been used hitherto to describe dermatitis occurring from superficial staphylococcal infection. Whether the infection is secondary to other skin pathology, as may occur in the hand (15) or is primary, as generally seems to be the case around the eyes, is relatively unimportant from the therapeutic viewpoint; in either event, specific anti-bacterial treatment in all its forms is indicated, in contrast to the nonspecific symptomatic therapy used for other types of eczema. Proper diagnosis is therefore of the utmost importance as such aggressive treatment wrongly applied to the hypersensitive skin of contact allergy, or to the acute manifestations of other dermatoses, will aggravate them immeasurably. The bland regime indicated in non-bacterial eczemas, on the other hand, if wrongly used in the infectious cases, merely serves to provide a better climate for the bacterial process.



FIG. 3. Staphylococcal eczema of the eyelid



FIG. 4. Staphylococcal eczema of the eyelids. Note the great superficial similarity to Figure 2, where the eczema was of non-bacterial origin.

Many unrecognized, recurrent cases of staphylococcal eczema of the eyelids are treated unsuccessfully for years as instances of contact allergy (16). One cannot distinguish between the two conditions on the basis of the character of the dermatitis as they look very much alike (Fig. 3, 4). What is required for the diagnosis and successful treatment of staphylococcal eczema is the demonstration that the focal point of the process is not the skin, but instead, is the eye and its adnexae. When this is demonstrated and proper treatment instituted, the eczema, which is, a secondary complication, gradually disappears. The key to the diagnosis is routine detailed ophthalmologic examination, both clinical and bacterial. This almost always will reveal the basis for the dermatitis, even if the primary focus is obscure, such as a minute abscess of a meibomian gland. The following findings differentiate staphylococcal eczema of the eyelids from the allergic variety: (a) blepharitis, with scaling, and often, ulcers of the eyelid margin; (b) meibomitis, either diffuse or focal; (c) superficial epithelial keratitis involving the inferior half of the cornea, readily seen on slit-lamp examination after staining with fluorescein, considered as pathognomonic of staphylococcal conjunctivitis (d) strongly positive conjunctival and lid margin cultures, showing many toxin-producing staphylococci, often entirely out of proportion numerically, to the objective clinical findings; and, (e) absence of eosinophiles in epithelial scrapings, which instead, usually reveal neutrophils and staphylococci, especially on the lid margins.

It should be emphasized that cultures of the lid margin and conjunctiva which are positive for pathogens (Fig. 5) are not a normal occurrence and serve to confirm the clinical findings, in patients suffering from staphylococcal dermatitis,



FIG. 5. Differential culture of the eyelid margins and conjunctivae obtained from the patient photographed in Figure 3, revealing innumerable toxigenic staphylococci. The bacteria growing in the form of "M" (at the top of the blood plate) was obtained from the meibomian glands.

that the primary trouble is ocular, not dermatologic. In this regard they are more significant than cultures of the involved eczematoid skin, because pathogenic staphylococci, which often are found on normal skin are especially common in all types of eczema.

The occurrence of staphylococcal eczema appears to require a special basic diathesis or set of circumstances. The dermatitis is found almost predominantly in middle-aged women, often post-menopausal. These patients, in the main, have very sensitive skins, exhibiting a marked tendency to develop multiple drug allergies. Mild hypothyroidism is not uncommon. Diminished lacrimation or even frank keratoconjunctivitis sicca may be present. The occurrence of mild hypothyroidism and, especially, a seborrheic diathesis, both with dry skins, appears to be more than coincidental. An interesting phenomenon is the presence of verrucous lesions which become prominent in these patients. It would appear that these factors, in addition to irritation from cosmetics, may predispose such patients, in the absence of atopy, to hypersensitivity or heightened susceptibility to bacterial products.

The concept that local infections by bacteria could cause eczema was not a new one at the time the apt, if unwieldy, term "infectious eczematoid dermatitis"



was given to the entity by Engman in 1902 (17). However, while others, before and after, did stress the role of bacterial infection in its causation, only recently has the importance of either primary or secondary bacterial infection, especially staphylococcal, in the production and perpetuation of eczema, become generally accepted. The important role the staphylococcus plays in the pathogenesis of many common external diseases was originally unappreciated because early investigators did not differentiate pathogenic toxin-producing strains from the ubiquitous non-pathogenic varieties to be found on cultures of the conjunctiva and other mucous membranes, the eyelids and the skin. The fact that the staphylococcus produced exotoxins and other toxic products was demonstrated more than fifty years ago; however, except for the French, these toxins received surprisingly little attention until 1929, when Burnet's (18) fundamental paper appeared. This work is the basis of modern concepts concerning these toxins, as well as for the therapeutic use of staphylococcal toxoid and antitoxin. In the field of ophthalmology Thygeson (19-21) was the first to stress the etiological importance of such toxigenic staphylococci in blepharitis, meibomitis, conjunctivitis, especially of the chronic variety, and in keratitis, revitalizing our concepts and treatment of these long-neglected conditions.

A dual mechanism appears to be responsible for the production of staphylococcal eczema. The first of these appears to be the direct toxic action of the dermonecrotizing, thermolabile and filtrable exotoxin of the staphylococcus. Both conjunctivitis and keratitis has followed the direct instillation of staphylococcus toxin (22, 23), and antitoxin has been successfully used in staphylococcal corneal ulcers that did not respond to antibiotic treatment (24). The second mechanism appears to be allergy to staphylococcal products, including staphylococcal exotoxins, edotoxins, and possibly staphylococcal protein itself (25-28). There appears to be no question that such allergy is common and may at times reach severe proportions. While new born infants do not show skin reactions to staphylococcal filtrates they occur in 65 per cent of normal individuals and in nearly all persons with staphylococcal infections. Since the reaction appears to develop without relation to the amount of antitoxin in the blood it would seem to indicate an allergic state. In my experience these skin reactions may be of both the immediate as well as of the delayed type.

The significance of positive reactions to intradermal injections of staphylococcus toxin or toxoid has not been universally accepted because so many persons, having been exposed to the staphylococcus at some time in their lives, exhibit a certain degree of sensitivity. However, recent investigations support clinical observation that marked reactions are of diagnostic value. Gernez and Pannequin (29) for example, feel that intradermal injections of toxin cause two phenomena, one toxic, the other allergic. The toxic reaction, being reciprocally dependent on the blood antitoxin titer provides an index of immunity to staphylococcus infection; the allergic reaction, which is of shorter duration, is uninfluenced by antitoxin and may be elicited by dilute toxin, heated toxin, or toxoid. The intradermal reaction to dilute toxoid offers, within limits, an index of allergy to staphylococcal proteins and to other staphylococcal products. While minor reactions



to the injection of dilute toxoid or vaccine may be of questionable value, it would appear therefore that marked reactions are diagnostically significant of allergy. An allergic correlation of positive toxoid reactions with past or present staphylococcal infections has been found by Wagner and Maly (30).

Other experimental work that would appear to support the thesis that a complex type of bacterial allergy plays a role in the occurrence of staphylococcal eczema is deduced from the studies of Hopkins and Burky (31), who successfully treated forty cases of intractable eczema with staphylococcus toxin. These patients all showed marked sensitivity on skin tests to this toxin and on culture most lesions revealed pathogenic staphylococci. They concluded that the dermatitis was due to a local hypersensitivity to the patient's own skin keratin, brought about by the liberation of staphylococcus toxin, plus trauma at the site of the lesions. This is confirmed to some extent by the work of Hecht, Sulzberger, and Weil (32) who, in 1943, showed that in the production of antibodies to homologous skin in rabbits, staphylococcus toxin exerted a synergistic action when injected coincidentally with rabbit skin antigen. Other studies such as those of Storek (33) and Ulbricht (34) also lead to the conclusion that bacterial sensitivity is a definite cause of eczema.

*Treatment of Staphylococcal Eczemas:* While the immediate objective of treatment as far as the patient is concerned, is to cure the eczema, the physician's goal should include the elimination of the underlying infection. This may prove very difficult. If it is not accomplished, however, recurrences of the dermatitis are not infrequent. Therapy is based primarily on the use of antibacterial agents and injections of toxoid and vaccines, when indicated. Such newer agents as the sulfonamides and the antibiotics, however, often are disappointing, due to the occurrence of bacterial resistance and the frequency of drug allergies. For this reason, the intensive use of antibiotics systemically, if tolerated, is indicated in the early treatment, but is not especially effective, unfortunately. Often the best results are obtained by expression of the lid margin glands for the elimination of the meibomitis and the topical application of 2 per cent silver nitrate to the lid margins, the entire involved skin of the eyelids and especially, on any fissures that may be present. Such antiseptics like 10 per cent sodium propionate (35, 36) which is unlikely to sensitize or irritate the skin of the eyelids, often are valuable. Hydrocortisone in the ointment form is the most effective of the cortico-steroids. Its local use often results in rapid improvement in the dermatitis, after the underlying bacterial process is controlled but not necessarily eradicated.

Resistant cases of staphylococcal eczema require injections of staphylococcus toxoid and/or vaccine. The best results are often obtained with a combination of both because the use of toxoid alone only results in increased titer of staphylococcus antitoxin but does not stimulate the formation of other types of antibodies such as agglutinins. Vaccines, on the other hand are less valuable antigenically in regard to antitoxin formation, but are superior in regard to the stimulation of other types of antibodies. The best therapeutic results with such biological therapy often occur in individuals with the most marked initial reactions. If

clinical improvement is paralleled by negative conjunctival and lid margins cultures and reduced intradermal reactions, recurrences are unlikely. However, even though the eczema is temporarily controlled by local therapy, should cultures and skin reactions remain positive, recurrences are to be expected. Although the antitoxin titer is usually elevated after vaccination, this is not always so; instances have been reported where minimal intradermal reactions to toxoid are present in previously positive individuals, despite a very low antitoxin titer (29).

It seems advisable to base initial dosages on the reaction to small intradermal injections, and to maintain a flexible schedule dependent on the individual's tolerance. Using staphylococcus toxoid, of which there are a number of varieties available, the original injection should be 0.01–0.02 cc. Until the amount used is more than 0.1 cc it should be injected intradermally, thereafter 0.1 cc of the dose may still be given in the same manner and the remainder of the dose is administered subcutaneously. Increasing slowly (0.1 cc at a time) injections are given once a week or every 4–5 days. Once dosage reaches 1.0 cc it may be given at increasing intervals, but should be maintained at that level for a long period of time to ensure a constantly elevated antitoxin titer in the blood. More rapid dosage schedules may be used, but generally slow increases appear preferable. Tasman et al (37) indicate that with a new purified and adsorbed toxin maximal antitoxin titers are attained after only a few injections, regardless of intervals between injections, with no undesirable side reactions.

#### ECZEMA OF THE EYELIDS IN GENERALIZED DERMATOSES

In certain generalized dermatoses, such as atopic dermatitis, neurodermatitis, psoriasis and especially seborrheic dermatitis, a non-specific type of eczema of the eyelids may occur. The distinguishing feature of these cases is, that while the eyelid may appear to be the only area of skin involved and the eye itself may show changes, careful search, however, will reveal diagnostic skin lesions elsewhere. Treatment of this type of non-specific eyelid eczema is gentle and soothing, in order to alleviate the acute reaction that is present.

*Atopic Dermatitis and Neurodermatitis:* Atopic dermatitis is an extremely pruritic condition with a predilection for the eyelids, face, the sides and back of the neck and both the ante-cubital and popliteal flexures, which occurs characteristically in the young. A familial history usually is obtained and other allergies such as hay-fever and asthma are either present or develop later on. Multiple atopic sensitivities of the "immediate" type are demonstrable upon intra-cutaneous or scratch testing, yet the agents responsible for the eczema are not demonstrable by these intra-dermal wheal tests. Blood eosinophilia often occurs. The eczema is characterized by exacerbations and remissions over the course of years. In long standing cases cataracts occur. Keratoconjunctivitis has recently been described (38) as a further manifestation of atopic eczema, paralleling the skin activity of the disease and characterized by thickening and hyperemia of the conjunctiva with opacification and vascularization of the cornea. Conjunctival eosinophilia is present. In these patients prompt improve-

ment occurred with oral or topical cortisone therapy. Atopic eczema responds to systemic steroid therapy but recurs when treatment is stopped.

Neurodermatitis appears in adults often without atopy, and is usually related to one circumscribed area.

*Seborrheic Dermatitis and Psoriasis:* Seborrheic dermatitis is a superficial scaling dermatitis of diffuse involvement rarely limited to the eyelids. Lesions occur typically in the scalp (dandruff), eyebrows, lid margins (Fig. 6), behind the ears, the sternum and axillae. Seborrheic blepharitis is characterized by greasy scales, which reveal numerous yeast (*Pityrosporum ovale*) on scrapings. An associated conjunctivitis may be present, but superficial epithelial keratitis only rarely occurs and is not likely to be confused with the staphylococcal variety. The dry skin of the eyelids of the seborrheic individual may serve as the predisposing factor in both allergic and infectious eczema.

Psoriasis favors the hair line of the scalp, elbows, knees and extensor surfaces of the extremities. The eyelids and face are rarely affected. Plaque-like, hyperemic, scaly, lesions occur. Ocular complications include blepharitis, conjunctivitis and keratitis. These are rather rare but do occur and are as resistant to therapy as the basic disease. They should be looked for in every case of psoriasis, but it is a fallacy to assume that every conjunctivitis or blepharitis encountered in patients with psoriasis is psoriatic in origin. Many such inflammations respond to the usual forms of treatment and have nothing to do with the skin disease.

*Treatment of Non-specific Types of Eczema:* The basic principle in the treatment of the acutely inflamed eyelid is a gentle and soothing, stage-by-stage, symptomatic approach. When edema and erythema are present, astringents are indicated,



FIG. 6. Seborrheic eczema of the eyelids

in the form of wet dressings. Chamomile tea or cold milk are the mildest; dilute aluminum acetate (1:20) and 2 per cent sodium propionate are also useful. After the acute signs have subsided (in 24 to 48 hours) and the condition becomes subacute, pastes are employed, since the further application of compresses would lead to excessive dryness and consequent fissuring. A paste is a mixture of powder and grease. Lassar's zinc paste, containing zinc oxide, talcum, lanolin, petroleum jellys and wax, is the one most commonly used. A paste being porous, due to the powder it contains, will cool the skin and adsorb the microscopic ooze that exists at this subacute stage; an ointment, being non-porous, will heat the skin and is not well tolerated. The paste is applied in a very thin film, morning and night. Soap and water should be strictly prohibited. If cleaning is desired, gentle sponging with olive oil is indicated. After several days of application an excessive dryness may develop. At this stage, when only minimal inflammatory signs are present, a mild ointment like petrolatum or boric acid ointment should be applied very thinly at night and removed, almost but not quite entirely (with dry cotton), in the morning.

Up to this point only bland medicaments are used. Pharmaceutically active drugs, such as sulfur, mercury, tar and vioform, are reserved for chronic infiltrated cases. The drugs should be prescribed in weaker concentrations than those used routinely on the other parts of the body. If a seborrheic basis is suspected sulfur 1 per cent to 2 per cent is indicated. Ammoniated mercury, 1 per cent to 2 per cent may be very effective in the seborrheic type where psoriasis plays a role. Vioform 1 to 2 per cent has proved generally valuable eczema and is especially effective where the lesions have an impetiginous character.

Fissures, which occur when the skin begins to dry, should be cauterized with silver nitrate 2 per cent. Then the medication, paste or ointment, is applied directly to the cauterized fissure to counteract the extreme dryness of the caustic.

Many drugs such as tar, sulfur and vioform are supplied in a vanishing cream base. Creams are thinner than ointments due to a greater content of fluid ingredients. Vanishing creams are soaps, being oil-in-water emulsions in which the fats have been saponified by suitable alkalies. They have a cooling effect because they evaporate yet do not dry to excess since a film of bland fatty soap remains. Vanishing cream bases embody in one preparation the three principles of treatment outlined above: (a) the moisture, for the acute stage, (b) the paste, for the sub-acute stage and (c) the softening grease, for the chronic stage. Thus they may be substituted in sub-acute or chronic cases with a reasonable degree of success, but the stage-by-stage approach described above is generally more advisable if the patient can be seen frequently enough.

#### SUMMARY

The management of eyelid eczema, at best presents problems. Many of these difficulties are, however, avoidable and may be attributed to the unfortunate tendency of almost always considering the dermatitis as allergic in origin and not recognizing that other conditions may present a superficially similar clinical



appearance. An incorrect diagnosis leading to faulty therapy not only will yield no benefit but can result in aggravation of the original dermatitis. Three main groups of eczema of the eyelids are encountered clinically: (a) allergic eczematous dermatitis, secondary to contact allergy, in which the basic treatment is elimination of the sensitizing substance, (b) staphylococcal eczema, secondary to eyelid infection, the most common cause of chronic eczema encountered by ophthalmologists, in which antibacterial agents and the use of staphylococcus toxoid and vaccine is indicated, and (c) certain generalized dermatoses such as atopic dermatitis, seborrhea and psoriasis, in which the non-specific eyelid eczema that occurs as part of the generalized dermatitis, requires a gentle stage-by-stage symptomatic approach.

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# THE EFFECT OF HEPATO-BILIARY DISEASES ON THE SERUM ACID PRECIPITABLE GLOBULIN (APG) TURBIDITY\*

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## INTRODUCTION

Hepatitis and portal cirrhosis are often associated with gamma globulinemia whereas chronic biliary obstruction usually results in beta globulinemia (lipoproteinemia) (1, 2). Thus, selective alteration in the distribution of the major serum globulin fractions may develop as a consequence of diverse hepatic or biliary tract diseases.

A convenient turbidimetric method for the estimation of the serum concentration of a group of alpha-2 plus beta globulins designated as "acid precipitable globulins" (APG) has been described in previous reports (3, 4, 5). The APG turbidity values from individual sera were quantitatively reproducible. Although the APG isolated by precipitation from normal or pathological sera consistently manifested the electrophoretic mobility of alpha-2 plus beta globulin, the composition of the lipoprotein complexes in APG showed considerable variation in the proportions of lipid, protein, and bound carbohydrate (polysaccharide). The APG turbidity level was enhanced in the presence of hyperlipemia and partially suppressed by marked increase in gamma globulin concentration. Changes in the serum albumin concentration failed to influence APG turbidity levels. Comparison of APG turbidity with paper electrophoretic patterns suggested that APG represented a major but apparently inconstant moiety of total estimated serum alpha-2 plus beta globulin concentration. Thus, the APG turbidity value, per se, appeared to represent an approximation or guide to the concentration of total serum alpha-2 plus beta globulin.

The conjoint estimation of the APG turbidity with Kunkel's (6) zinc sulfate (ZS) turbidity procedure (for estimation of serum gamma globulin concentration) permitted an assessment of broad alterations in the globulin spectral pattern. The globulin fractions measured by these two turbidity procedures showed little overlapping. The derived ratio APG/ZS provided a more accurate correlation of turbidity data with gross shifts in relative or absolute preponderance of either of the two large electrophoretic groups of serum globulins, i.e. the alpha-2 plus beta globulin versus the gamma globulin fractions.

Increased serum APG turbidity levels have been recently described in patients with obstructive biliary disease (3) or advanced disseminated neoplasms (4). These observations have now been extended to include the determination of APG and ZS turbidity and the APG/ZS ratio in over 170 patients with hepatog-

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enous or obstructive jaundice. The foregoing data on the APG turbidity in jaundiced patients have also been supplemented by a general experience in over a thousand patients with diverse medical disorders.

#### MATERIAL AND METHODS

The APG turbidity procedure was performed as follows: One-tenth ml of serum was diluted 1:60 with an acidic (pH 4.42) acetate low ionic strength buffer containing 130 mg. (0.14 ml) of glacial acetic acid and 136 mg. (1.0 ml. of 1 molar solution) of sodium acetate per liter. After allowing the diluted serum to stand for 30 minutes at room temperature, turbidity was estimated at 650 mu. in a Coleman Jr. spectrophotometer.

The zinc sulfate turbidity procedure was performed as described by Kunkel (6). Kunkel's (6) twenty unit standard turbidity suspension\* was employed for both the APG and ZS turbidity procedures. Determinations were performed in specimens obtained in the fasting state. Fresh sera or sera promptly frozen once and freshly thawed were employed. Buffer for the APG procedure was prepared once per week or was discarded whenever pH exceeded  $4.42 \pm 0.02$ ; for the Kunkel buffer, whenever pH exceeded  $7.5 \pm 0.10$ . Other details of the methods employed have been provided elsewhere (5, 6, 7, 8, 9).

The clinical material obtained for study represented almost all patients with hepatogenous or obstructive jaundice hospitalized on the medical wards of the Mount Sinai Hospital during a one year period. Clinical diagnoses were established by various members of the house and attending staffs not directly associated with this study. The diagnosis of neoplastic disease was established by tissue biopsy or autopsy examination in all instances.

Clinical diagnoses were confirmed by laparotomy in approximately three-fourths of the patients with inflammatory biliary tract disease. Liver aspiration was employed in a small number of the patients with hepatitis or portal cirrhosis.

#### RESULTS

Table I summarizes the APG and ZS turbidity values and the APG/ZS ratio in the initial serum sample obtained from 178 patients hospitalized with various types of hepatogenous or obstructive jaundice. The data were analyzed with a normal range for the APG and ZS turbidity of 4-8 units; for the APG/ZS, the normal range extended from 0.6-1.8. No attempt was made to correlate these data with the stage of hepatic or biliary disease when the first serum sample had been obtained. Post-operative sera were excluded from this report. Serial studies illustrating fluctuations in these turbidity indices during the course of disease and their relationship to the serum mucoprotein (7, 8) and the total bound polysaccharide (9) will be presented in detail elsewhere (10).

\* (3 ml. of 0.0962 normal  $\text{BaCl}_2$  diluted to 100 ml with 0.2 normal  $\text{H}_2\text{SO}_4$ ; take 5.4 ml. of this freshly prepared  $\text{BaSO}_4$  solution and dilute with 0.6 ml. of 0.2 N  $\text{H}_2\text{SO}_4$  to yield a fresh relatively reproducible standard. A ten unit standard is made with 2.7 ml of  $\text{BaSO}_4$  and 3.3 ml of  $\text{H}_2\text{SO}_4$  solution. From the two points a straight line curve may be constructed and readings converted directly.



TABLE I

*The Serum Acid Precipitable Globulin (APG) Turbidity; the Serum (ZS) Turbidity and the APG/ZS in Initial Sera from 178 Consecutive Patients with Hepatogenous or Obstructive Jaundice*

Diagnosis	No. Patients	APG			ZS			APG/ZS		
		Low*	% Normal	High	Low	% Normal	High	Low	% Normal	High
I. Hepatitis . . . . .	37	0	81	19	5	8	87	57	38	5
II. Portal Cirrhosis . . . .	51	43	47	10	2	14	84	86	10	4
III. Obstructive jaundice										
Carcinoma of pancreas or gall-bladder . . . . .	21	0	5	95	33	52	13	0	33	66
Cholecystitis, common duct stone, cholangitis, pancreatitis, biliary cirrhosis	44	0	41	59	20	61	19	4	55	41
IV. Jaundice from extrabiliary primary neoplasms										
Obstructive metastases or metastatic hepatomegaly . . . . .	25	0	28	72	20	40	40	16	44	40

Normal range: APG = 4 to 8 units; ZS = 4 to 8 units; APG/ZS = 0.6-1.8.

### *APG Turbidity*

Among thirty seven-patients with homologous serum or infectious hepatitis, the initial APG turbidity values were normal in 81 % and increased in 19 %. As can be seen from the graphic representation (Fig. 1), no hepatitis serum initially showed a reduced APG level and in only one serum did the APG value exceed 12 units. In contrast to the absence of low APG values in the initial hepatitis sera, there were 43 % low APG values among 51 patients with portal cirrhosis. As in the hepatitis sera, a relatively small number, only 10 % showed any increase in the APG value (i.e. >8.0 units), and there were no values over 10 units. Thus among the total hepatitis-portal cirrhosis group, less than 15 % showed any increase in APG value, a value above 10 units was rarely exceeded, and about half of those with portal cirrhosis showed reduced APG values (i.e. <4.0 units).

This preponderance of normal or low APG turbidity values in hepatogenous jaundice contrasted with the incidence of increased APG values in patients with obstructive jaundice. Not a single low APG value was found among the total of 90 patients with obstructive jaundice. An incidence of 95 % high APG values was found in the series of 21 patients with carcinoma of the pancreas. Increased APG values were also found in 50 % of inflammatory biliary tract disease patients and in 72 % of patients with non-biliary or non-pancreatic neoplasms producing obstructive metastases or metastatic hepatomegaly with jaundice. The significance of this frequency of normal or low APG values in hepatogenous jaundice and of high APG values with obstructive jaundice was enhanced by a reciprocal distribution of the ZS turbidity values among the same groups of patients studied.

### *Zinc Sulfate Turbidity*

The incidence of increased gamma globulin, as measured by ZS values above 8.0 units, was approximately equal (Table I, Fig. 2) in the two groups of hepatogenous jaundice, i.e. 87 % among those with hepatitis and 84 % among those with cirrhosis. However, forty per cent of patients with metastatic carcinoma with jaundice also showed some increase in ZS turbidity as did 18 % of inflammatory biliary disease and 13 % of pancreatic carcinoma cases. It was noted that values greater than 15 ZS turbidity units occurred in only 4 of 90 patients with obstructive jaundice due to various causes, whereas ZS values above 15 occurred in about half of the hepatitis-cirrhosis group. The ZS turbidity values were normal in from 40 to 60 % and low in from 20 to 33 % of all patients with obstructive jaundice, whereas among the hepatitis-cirrhosis groups only 8 to 14 % normal values and 2 to 5 % low values were observed in the initial serum sample.

### *The APG/ZS Ratio*

An apparent preponderance of alpha-2 plus beta globulin compared to gamma globulin expressed as an increased APG/ZS ratio ( $>1.8$ ) occurred in 66 % of the initial sera obtained from pancreatic carcinoma patients (Table I, Fig. 3). Normal ratios (0.6-1.8) were found in the remaining 33 %. Low APG/ZS ratios were not found in either the initial (or subsequent) sera from any patient with pancreatic carcinoma. These findings were in distinct contrast with the preponderance of gamma globulin as indicated by low APG/ZS ratios in 57 % of the hepatitis cases and in 86 % of the patients with portal cirrhosis. A low APG/ZS ratio was found in only 4 % of the patients with inflammatory biliary disease and in 16 % of those with metastatic neoplasms (cases of x-ray treated lymphoma and jaundice). Thus in the initial 88 hepatitis or portal cirrhosis cases there were about 75 % low APG/ZS ratios, 20 % normal ratios and 5 % high ratios when first studied, whereas among the total group of 90 cases of obstructive jaundice about 50 % had high APG/ZS ratios, 40 % had normal ratios and only 10 % had low APG/ZS ratios.

The gradient of the shift in globulin distribution observed by employing these turbidity procedures in hepatogenous or obstructive jaundice was graphically represented in Fig. 4. Although the range of values for each of the five groups of patients overlaps (Figs. 1-3) it may be noted that the median value of the APG turbidity in carcinoma of the pancreas was three fold higher than that seen in portal cirrhosis. Reciprocal three-fold differences among the medians for the hepatogenous and obstructive jaundice groups were also observed with the ZS turbidity values. The median for the APG/ZS ratio showed a greater spread than the medians for either turbidity procedure alone i.e., five fold differences.

### *Relative Selectiveness of APG and ZS Turbidity Procedures*

During the course of these studies on the APG turbidity procedure in jaundiced patients a total of 1820 individual determinations of serum APG and ZS turbidity performed were on 1047 patients with diverse medical disorders. Table II sum-

marizes the relative selectiveness of these procedures in patients who at any time, i.e., on initial or serial sera, had APG or ZS turbidities of 4 units or lower or 10 units or higher. The random observation of a low serum APG turbidity value was found to be associated clinically with hepatitis or portal cirrhosis in 36 of 68 patients, i.e., in approximately 60 % of the low APG values observed in this clinical survey. Low ZS turbidity values were found in 200 patients of which 45 or 23 % were suffering from biliary obstruction. About 40 % of patients who on a random specimen showed a high APG turbidity value were found to have biliary

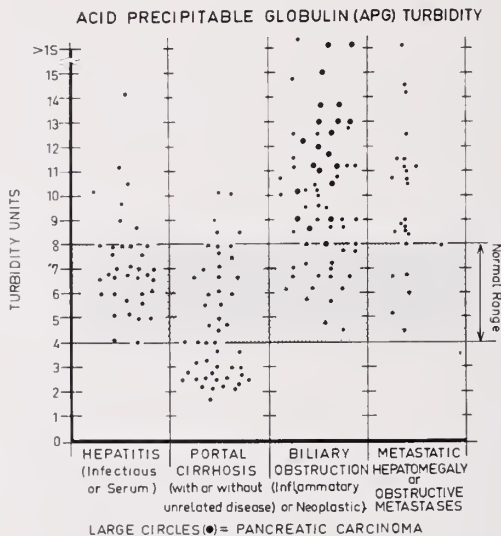


FIG. 1

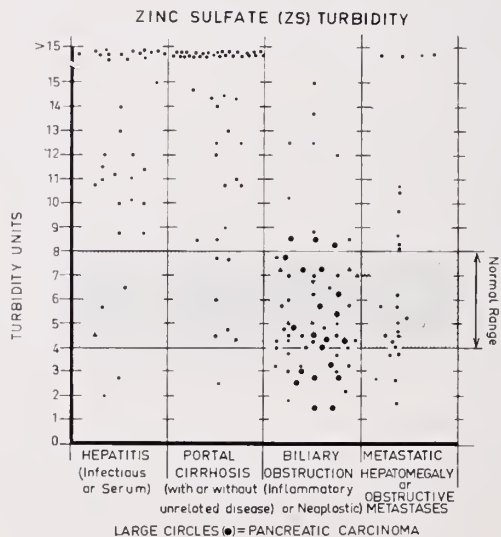


FIG. 2

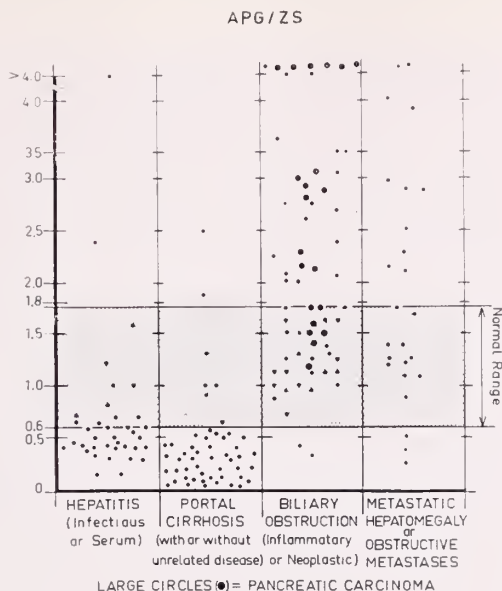


FIG. 3

FIGS. 1-3. The APG turbidity, the ZS turbidity, and the APG/ZS respectively in initial sera from 178 patients described in Table I.

obstruction, and about an equal proportion with high ZS values had hepatitis or portal cirrhosis. From these observations it also appeared that the APG turbidity approximated the ZS procedure in value as an aid in the differential diagnosis of jaundice in the patient population under study.

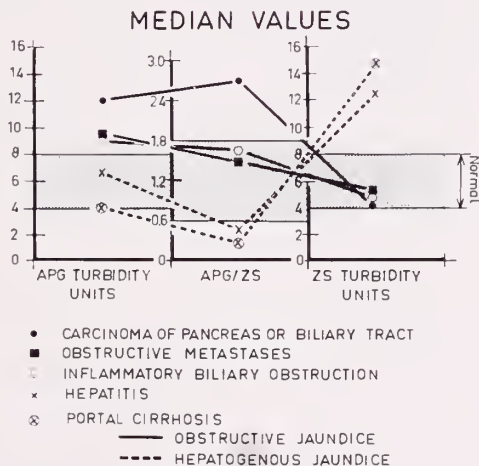


FIG. 4. Representation of the shift in serum globulin distribution patterns as estimated from the turbidity procedures in patients with jaundice of varied etiology. Median values for each clinical group are shown. The APG/ZS showed a wider difference between the medians for each group than did either the APG or ZS turbidity alone.



TABLE II

*The Relative Selectiveness of Abnormal Serum APG or ZS Turbidity in 1825 Sera from 1047 Patients with Diverse Medical Disorders*

Turbidity Value	Total Patients†	Patients with Hepatitis or Portal Cirrhosis	Patients with Biliary Obstruction
APG > 10 units with significant increase in alpha globulin indices* . . . . .	97	0	20
APG > 10 units without increase in alpha globulin indices . . . . .	76	2	32
ZS from 10-15 units . . . . .	141	29	20
ZS > 15 units . . . . .	136	75	1
APG < 4.0 units . . . . .	67	36	3
ZS < 4.0 units . . . . .	200	5	45

\* Serum mucoprotein greater than 80 mg% with total bound polysaccharide greater than 140 mg%.

† Patients who at any time during hospitalization showed turbidity values beyond indicated range.

#### DISCUSSION

The clinical usefulness of the zinc sulfate turbidity procedure devised by Kunkel for estimating serum gamma globulin concentrations has been established (6). Although at least 80 % of patients with hepatogenous jaundice may be expected to show increased ZS values, a disconcerting number of patients with surgical jaundice, in our study about 25 %, also manifested some degree of elevation of ZS turbidity, usually not above 15 turbidity units. When the APG turbidity was estimated and its relationship to the ZS turbidity expressed as the APG/ZS ratio, the apparent differential value of the combined turbidity procedures, was greater than was observed with the ZS turbidity alone. Thus by employing the relative amounts of beta to gamma globulin, rather than the absolute concentration of gamma globulin, to detect the "pure" gamma globulinemic serum characteristic of hepatogenous jaundice, there were only 5 % false positives, i.e., low APG/ZS in the obstructive jaundice group, compared with an incidence of 25 % false positives, i.e., high ZS turbidity using the ZS value alone in the same group of jaundiced patients. When a high APG/ZS ratio in obstructive jaundice was compared with low ZS turbidity alone, the advantage in performing the two turbidity procedures was again noted, namely 50 % high APG/ZS ratios were found in contrast to 25 % low ZS values. These data express the added potential value obtainable by performing the APG turbidity procedure conjointly with the ZS turbidity in the differential diagnosis of jaundice.

Despite the fact that increased serum APG turbidity levels were commonly found in the presence of biliary obstruction, an increased APG turbidity level per se cannot be considered as a specific sign of biliary obstruction. Increased concentrations of APG reflect changes in either alpha-2 globulin, beta globulin or both. The relative proportions of either of these two globulin fractions are known to differ not only between normal males and females (11), but also be-

tween normals and patients with arteriosclerosis (11), as well as in patients with proliferative diseases, on the one hand and biliary obstruction on the other (10). In biliary obstruction the relatively carbohydrate-poor (polysaccharide) beta fraction would be expected to produce the increment resulting in increased APG turbidity levels, whereas an increase of the polysaccharide-rich alpha-2 globulin component in the presence of widespread proliferative processes (inflammatory or neoplastic) would be expected to also result in increased serum APG turbidity levels. When biliary obstruction is accompanied by extensive inflammatory or neoplastic tissue changes there would be expected to be an increase in both alpha-2 and beta globulin components. The association of non-jaundiced advanced neoplastic disease with high APG levels has already been reported (4). High APG levels in these cases were usually accompanied by high alpha-1 mucoprotein, and a high total protein bound polysaccharide concentration contributed by a large increase in the carbohydrate-rich alpha globulins. Thus, the globulin response in biliary obstruction may be expected to depend on the nature, duration, and extent of the pathologic process.

In problems of differential diagnosis of jaundice, the APG turbidity procedure seems to afford a useful aid in detecting changes of potential differential diagnostic significance in the alpha-2 and beta portions of the globulin spectrum—an area of the globulins not heretofore easily measured by simple laboratory techniques.

#### SUMMARY

The potential diagnostic value of the serum acid precipitable globulin (APG) turbidity, a simple estimate of alpha-2 plus beta globulin concentration, was investigated in 174 patients with hepatogenous or obstructive jaundice. Low APG turbidity was noted among half of the portal cirrhosis cases; normal APG turbidity levels (4–8 units) were observed among 85% of hepatitis sera. Less than 15% of the hepatitis-portal cirrhosis group showed an increase in APG turbidity. This contrasted with the observation of increased APG turbidity in 95% of pancreatic or biliary carcinoma patients as well as in about two-thirds of patients with inflammatory biliary obstruction or obstructive metastases.

When the zinc sulfate turbidity (ZS) of Kunkel was employed conjointly to estimate serum gamma globulin concentrations, a derived ratio: APG/ZS provided a measure of the relative preponderance of alpha-2 plus beta globulin over gamma globulin or vice versa. In the hepatitis-portal cirrhosis group there were 75% low APG/ZS, 20% normal APG/ZS (0.6–1.8), and 5% high APG/ZS whereas in the obstructive jaundice group, there were 50% high APG/ZS, 40% normal APG/ZS, and 10% low APG/ZS. The most marked differences in APG turbidity levels were observed between patients with portal cirrhosis and those with pancreatic or biliary carcinoma.

The APG turbidity compared favorably with the ZS turbidity in simplicity and appeared to represent a useful aid in the detection of abnormal globulin distribution patterns in patients with hepatobiliary diseases.

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# THE ACID PRECIPITABLE GLOBULIN (APG) TURBIDITY: A CONVENIENT GUIDE TO THE STATUS OF SERUM ALPHA-2 PLUS BETA GLOBULINS\*

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## INTRODUCTION

Although simple turbidimetric techniques (1, 2) for the estimation of serum gamma globulin concentrations are now available for clinical use, analogous techniques for the determination of alpha globulins have not yet been established. Serum alpha-globulins might be measurable turbidimetrically if their precipitation behavior were clearly distinguishable from other major groups of serum proteins, particularly gamma globulin and albumin. Kunkel's zinc sulfate procedure (1) for the estimation of gamma globulin concentrations depends upon selective precipitation (turbidity) developed under conditions of pH (7.5) close to the isoelectric point of gamma globulins and at a low ionic strength. Since the most acidic proteins of the serum are among the alpha globulin fractions, an investigation of protein turbidity at a pH below 5 was undertaken in the hope of developing a simple technique for separation and estimation of serum alpha globulins. This paper describes a technique for the quantitative measurement of the concentration of a group of proteins designated (3, 4) as "acid precipitable globulin" (APG). APG consistently manifested the electrophoretic mobility of alpha-2 plus beta globulin, and appeared to represent a major moiety of the serum alpha-2 plus beta globulins.

While this study was in progress, Jacox (5) reported that by employing a detergent and adjusting conditions of pH and salt concentration it was possible to estimate by turbidimetric methods the concentrations of three major groups of serum proteins, i.e., albumin, gamma globulin, and "alpha-1 plus alpha-2" globulin. Jacox's method for measuring the latter differs in various details from the procedure described below for measuring the acid precipitable globulin (APG) and deals with a larger and broader group of globulins. It should be emphasized that, as is true of other established turbidimetric method for quantitative estimation of gamma globulin (1, 2) neither the foregoing method for estimating alpha-2 plus beta globulin (APG), nor Jacox's method (5) for "alpha-1 plus alpha-2" can be quantified precisely in terms of electrophoretic concentration equivalents, particularly in the presence of *extreme* changes in the concentration of other accompanying serum protein. Nevertheless, the present report suggests that the determination of serum APG turbidity and its relation to the zinc sulfate (gamma globulin) turbidity may offer a useful approach to the detection of relative or

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absolute alteration in the "globulin spectral pattern" with reference to the alpha-2 plus beta globulin fractions.

#### METHODS

To determine whether turbidity from gamma globulin was extinguished at an acid pH, 200 sera, from patients with diverse pathological conditions, which exhibited zinc sulfate turbidity values from 0.5 to 36.0 Kunkel units were tested at pH 4.5-4.6 employing an aqueous sodium barbital-barbituric acid solution (210 and 280 mg. respectively liter plus 24 mg. zinc sulfate/liter). One-tenth ml. of serum was diluted 1-60 with this acidic barbital solution, which had an ionic strength (0.01) as low as that employed by Kunkel (1) to develop gamma globulin turbidity. Turbidity was estimated at 650 mu. in a Coleman Jr. Spectrophotometer. When the turbidity procedure had been thereby shifted to the acid pH range and compared with the turbidity obtained with the Kunkel procedure at pH 7.5, there was a relative reduction in turbidity in some sera and an increase in others. Among an initial group of 200 studied, most sera with the higher turbidity values at acid pH showed normal or low gamma globulin turbidity, and vice versa. However, certain sera conspicuously failed to show the generally inverse relationship between gamma globulin turbidity and turbidity at the acid pH. Human gamma globulin\* solution yielded no turbidity when diluted at the acid pH. Zinc sulfate was eliminated from the test conditions since it failed to influence turbidity at the low pH range. The barbital solution, a poor buffer in the acidic range, was replaced by acetate buffer (v. i.).

An acetate buffer composed of 130 mg. (0.14 ml) of glacial acetic acid and 136 mg (1.0 ml of 1 M solution) of sodium acetate per liter was freshly prepared. The pH of this buffer remained at  $4.42 \pm 0.02$  for two to three days. Buffer solutions were discarded if the pH rose above 4.45. The protein precipitated when 0.1 ml of serum was diluted 1:60 by this buffer was designated as "acid precipitable globulin" (APG).

APG determinations were performed on fresh sera or promptly frozen sera freshly thawed once. Kunkel's twenty turbidity unit standard suspension (1) containing 3 cc. of 0.0962 N.  $\text{BaCl}_2$  diluted to 100 ml. with 0.12 N  $\text{H}_2\text{SO}_4$  was employed for both the APG and the zinc sulfate turbidity procedure. Turbidity was measured at 650 mu. in the Coleman Jr. Spectrophotometer after allowing diluted sera to stand at room temperature for 30 minutes. No significant variation in APG turbidity was observed when the interval during which the tubes were standing varied from 2.5 to 45 minutes. Contamination of buffer with mold produced a rising pH. Old sera, or poorly refrigerated sera with bacterial contamination showed unstable APG values. APG values from oxalated plasma were comparable with values in serum but heparinized plasma or heparinized serum showed marked increases in APG turbidity.

In an attempt to identify APG protein, a number of isolated protein fractions with known proportion of albumin, alpha, beta, or gamma globulins were tested turbidimetrically after dilution with the acetate buffer. At concentration of 3 to

\* 2% Squibb gamma globulin.

6% it was found that albumin (Cohn Fraction V), gamma globulin (Fraction II), and the small alpha-1 mucoprotein prepared by Cohn's (6) method (Fraction VI-6) or the Winzler method (7) failed to produce turbid solutions when diluted in the acid buffer. Fraction I produced a small amount of turbidity which could not be accounted for on the basis of its 60% content of fibrinogen since there were no significant differences between the APG values of sera when compared to oxalated plasma. That the slight turbidity from Fraction I was due to its 8% of alpha and/or 15% beta globulin content was suggested by the much higher turbidity values produced by fractions yielding a primary and relatively pure separation of alpha- and beta globulins, namely Fraction IV-1, Fraction IV-4. The small subfractions (6) of Fraction IV containing the lipid-free esterase (Fraction IV-6) and the beta-1 metal combining globulin (IV-7) failed to yield any significant turbidity.

Confirmation that APG was composed of alpha-2 plus beta globulin was obtained by electrophoretic (Tiselius) identification performed on a pooled APG sample obtained by centrifugation of freshly precipitated normal or pathological sera at high speed. From the schlieren (Tiselius) pattern\* of this APG sample in veronal buffer it was calculated that 94% of protein centrifuged under conditions of the APG turbidity procedure was composed of a major component which exhibited the mobility of an alpha-2 globulin, although a small shoulder within the major peak suggested the presence also of an accompanying beta fraction. Paper electrophoretic patterns of individual APG samples† obtained from normal or pathological sera (Figs. 1 & 2) showed that the major component of APG was consistently composed of alpha-2 plus beta globulin with little or no albumin, alpha-1 globulin, or gamma globulin.

#### RESULTS

The mean and standard deviation of serum APG values among forty normal subjects, ages 20 to 40, were  $6.1 \pm 0.6$  units with a range of 4.1 to 8.2 units. Values among males and females showed no significant differences. Since the range of values within 95% limits among the normals was 4.2 to 7.9, a convenient proximate range of normal values from 4.0 to 8.0 units was adopted.

To determine whether APG turbidity units values were equivalent to a given concentration of protein obtainable after precipitation of APG from diluted sera, the correlation of turbidity units with concentration of biuret-reacting protein in centrifuged APG was investigated in normal or pathological sera. From Fig. 3 it may be estimated that one unit of turbidity had a mean equivalent value of about 90 mg% of protein. This estimate was unreliable since the protein-equivalent values varied widely as the APG value of the sera increased. Thus, among four sera with APG values of 13 units, the protein content varied from 400 to 1350 mg% (Fig. 2). This wide range in the proportion of lipid to protein

\* Kindly performed by Dr. N. Weissman, Chief Chemist, Mainonides Hospital, Brooklyn, N. Y.

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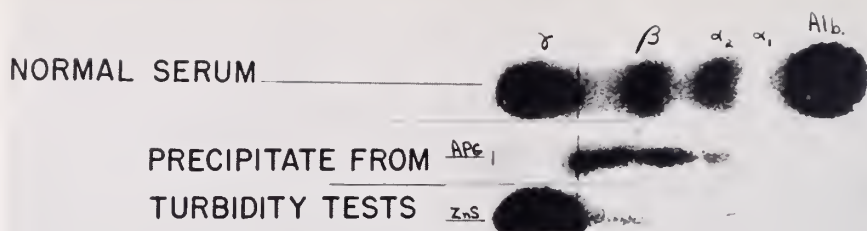


FIG. 1. Protein stained (bromphenol blue) paper electrophoresis patterns of a normal serum and the precipitates derived by centrifugation after performing the APG and zinc sulfate turbidity procedures.

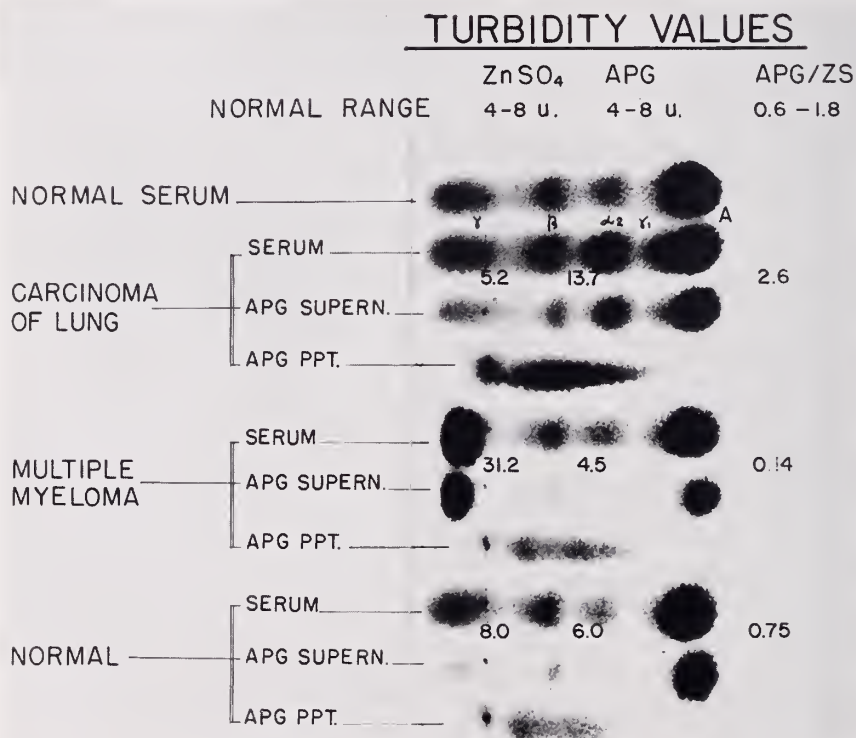


FIG. 2. Three serum patterns accompanied by values for the APG, and zinc sulfate turbidities and the ratio of APG to zinc sulfate turbidity. Below each serum pattern are also shown the pattern of its respective serum supernatant after precipitation of the APG. The supernatant was reduced to its volume prior to dilution by dialysis against polyvinylpyrrolidone. The APG after precipitation was dissolved in veronal buffer.

in APG was deemed to reflect differences in the proportion of alpha-2 and beta fractions. In a small number of sera studied, the content of galactose-mannose polysaccharide varied from only 1.9 to 2.9%, whereas the per cent of total lipid in the APG varied from 7.8 to 53.4%. Intrinsic technical error did not account

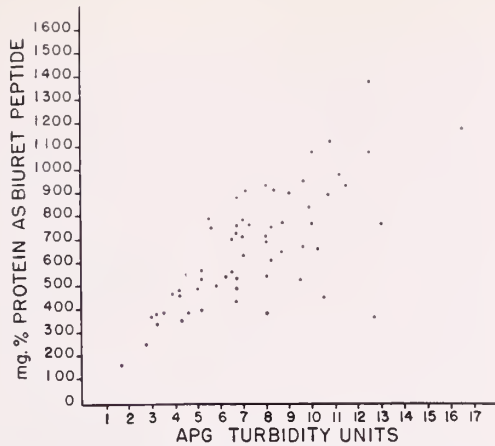


FIG. 3. The serum APG turbidity value plotted against the protein content of the APG obtained per ml. of serum by centrifugation from 59 diverse sera. No precise regression line can be drawn to obtain an approximate conversion factor for protein unit equivalents over the entire range of APG turbidity values.

for any significant variation in turbidity protein equivalents since a straight line (Beer-Lambert) relationship of optical density (APG values) to serum concentration of an high APG serum was obtained after mixing varying proportion of a normal serum with an extremely high APG serum.

The precise translation of APG values into concentration equivalents of alpha-2 plus beta globulin was precluded not only by this variation in lipid-protein ratios within the APG but also by the gamma globulin concentration of tested sera. Whereas the addition of albumin in increasing amounts resulted in no significant changes in APG values of a given serum, the addition of serum globulin up to final concentrations seen clinically in cases of marked hyperglobulinemia resulted in a limited but progressive reduction (Fig. 4) in APG turbidity. Thus, it appeared that extreme increases in gamma globulin, such as occurs in some patients with portal cirrhosis, sarcoid or multiple myeloma, might be expected to suppress APG turbidity to a limited extent (without necessarily affecting alpha-2 plus beta concentrations as estimated by electrophoresis).

Despite these factors which interfered with precise quantitative conversion of APG values into electrophoretically estimated alpha-2 plus beta globulin concentrations, there was a surprisingly good correlation (Fig. 5) between APG turbidity values and the visual estimation from paper electrophoretic patterns of the alpha-2 plus beta globulin concentrations. Among 33 sera chosen for study because of an expected diversity in pathologic globulin patterns accompanied by APG elevated above 8.0 turbidity units, there were 26 instances of 1-plus or greater increases and only one instance of a decrease in estimated alpha-2 plus beta concentrations. Twenty-three of twenty-four sera in which the alpha-2 plus beta concentrations were 2-plus or higher also showed an increased APG value. The single serum showing a 2-plus increase in alpha-2 plus beta globulin without a high APG value manifested a bizarre globulin pattern virtually devoid of gamma fractions. Only one specimen among 13 sera with reduced APG values



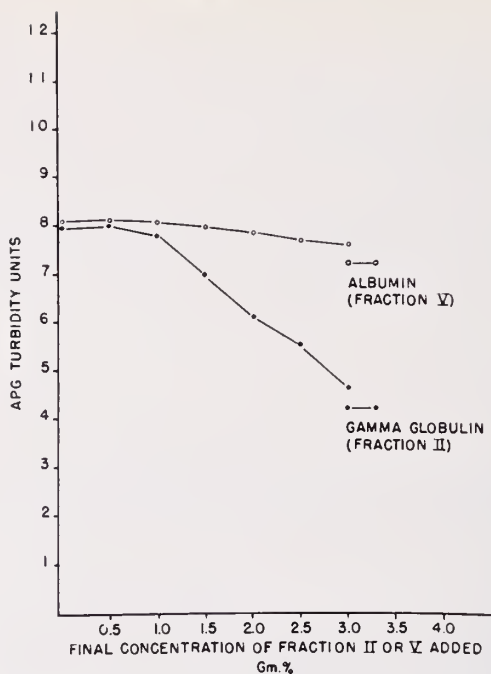


FIG. 4. Influence of added albumin or gamma globulin to the APG turbidity value of a normal serum. A limited suppression of APG turbidity was demonstrable after addition of relatively large amounts of gamma globulin.

(below 4.0 units) showed an increased estimated alpha-2 plus beta globulin concentration whereas 9 of the 13 showed reduced concentrations. There was a single serum with a high APG value despite an apparent reduction in alpha-2 plus beta content. This serum was characterized by a marked lipemia (total lipid of 3,000 gm %) which probably influenced the APG value without being reflected on the protein stained paper pattern. It was noted that sera with minimal increase (1-plus) in alpha-2 plus beta content showed (Fig. 5) a rather similar mean and range of APG values as did those without any recognizable change in alpha-2 plus beta pattern. This was possibly related to the finding that among the group of 26 sera with 0 or 1 plus alpha-2 plus beta content, 18 sera showed some increase in gamma globulin (zinc sulfate) turbidity. Thus, some of the inconsistencies in correlation of minimal changes in apparent alpha-2 plus beta concentration with the APG value could have been the resultant not only of differences in staining affinity based on variable lipid content of APG, but also as the consequence of the limited influence of gamma globulin concentrations on APG turbidity levels.

The foregoing observations suggested that the conjoint determinations of the APG turbidity procedure and the zinc sulfate turbidity might provide a more satisfactory index of relative or absolute changes in the alpha-2 plus beta globulin concentration. The ratio of APG turbidity to zinc sulfate turbidity (APG/ZS) was investigated among normal and pathological sera. The APG/ZS ratio varied from 0.6 to 1.8 with a mean and S.D. of  $1.06 \pm 0.33$  among 40 normal adult

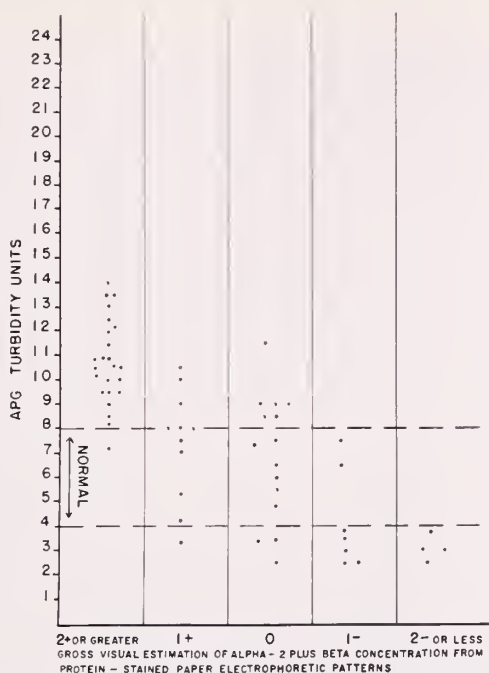


FIG. 5. APG values of sera plotted against gross visual estimation of alpha-2 plus beta concentration from paper electrophoresis patterns stained for protein with bromphenol blue (see text for details).

subjects. Among 39 pathological sera with APG/ZS ratios beyond these limits (Fig. 6), the paper electrophoretic patterns of 36 sera conformed to an expected relative or absolute preponderance of either alpha-2 plus beta globulin or gamma globulin. Among thirteen sera with normal globulin patterns (stained for protein with bromphenol blue) eleven showed normal APG/ZS ratios. Among 23 pathologic sera with normal APG/ZS ratios, only 2 showed marked relative shifts (2+ or greater) in globulin pattern which were not detected by the APG/ZS ratio. Among 8 sera with slight increases (1 plus) in visually estimated alpha-2 plus beta globulin concentrations five showed normal APG/ZS ratios. The failure of one serum with a markedly abnormal ratio to show an expected preponderance of alpha-2 plus beta globulin was attributed to an unusually large non-stained lipid moiety in the APG, associated with a marked lipemia.

The relationship of the APG to three other indicators of change among alpha and beta globulins, namely the serum mucoprotein content (8), the protein bound polysaccharide (9) and the thymol turbidity (10) was also investigated. Although the serum mucoprotein level and the protein bound polysaccharide were increased in most sera with high APG turbidity, many sera failed to show any parallel changes between these two constituents. No correlation whatsoever was noted between the thymol turbidity and APG turbidity values. In serial studies on individual patients, the mucoprotein, protein-bound polysaccharide and the thymol turbidity were found to vary independently of the APG turbidity.

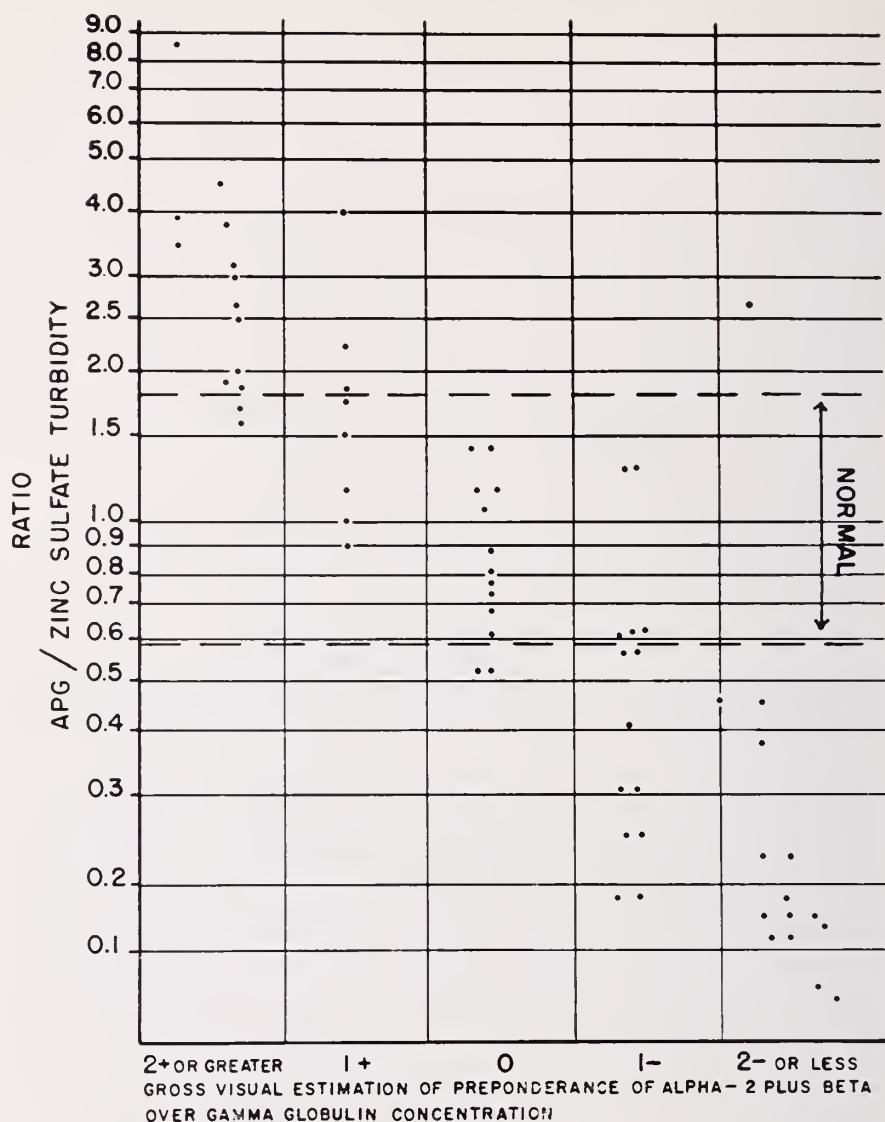


FIG. 6. The ratio of APG to zinc sulfate turbidity plotted against the gross visual estimation of the relative proportion of alpha-2 plus beta globulin to gamma globulin concentration of 51 serum paper electrophoresis patterns stained for protein with bromphenol blue.

Investigations of the clinico-pathological significance of the serum acid precipitable globulin (APG) index and the APG/Zinc sulfate turbidity ratio is published elsewhere (11).

#### DISCUSSION

The turbidimetric procedure elaborated for isolating the serum acid precipitable globulins (APG) provides a convenient index of the concentration of a

group of precipitable alpha-2 and beta globulins. It is likely that considerable variation in the composition of APG may be expected in diverse pathological states, despite the fact that APG appeared to be consistently composed of a major portion of the total serum alpha-2 and beta globulins. The APG turbidity procedure, in common with the zinc sulfate turbidity (1, 2), the thymol turbidity (10) and other protein turbidimetric procedures (5), exhibits an unfortunate inherent element of unreliability in that any turbidity observed may be influenced within limits by marked changes in the concentration and distribution of certain accompanying serum protein fractions which themselves do not precipitate under conditions of the procedure. As an aid in recognizing the indirect influence of abnormal gamma globulin concentrations, the APG/Zinc sulfate turbidity ratio, obtainable from 0.2 cc. of serum by rapid simple techniques, appeared to offer a convenient means of detecting gross relative or absolute shifts in the globulin spectral pattern.

In attempting to evaluate the relative accuracy of a turbidimetric procedure vs electrophoretic estimation of alpha or beta globulin fractions, an important complicating factor is the tendency for globulins of this part of the serum protein spectrum to become altered by coprecipitation, enzyme, and bacterial influences resulting from slight changes in handling or improper storage of sera. Additional difficulty in quantitatively comparing APG turbidity with paper electrophoretic patterns would seem to be the consequence of different dye-binding capacities of the various lipid rich proteins in the alpha and beta fractions and the fact that protein staining techniques (12) may not record with fidelity the optical property of the alpha-2 and beta lipo-protein complexes. Therefore, the measurement of APG turbidity can at best be taken only as a crude guide to the quantitative status of the alpha-2 plus beta globulins. Nevertheless, the APG turbidity procedure seems to offer data sufficiently quantitative as to represent a potential clinical aid analogous to procedures employed clinically for estimating gamma globulin and other serum protein components.

#### SUMMARY

Turbidity resulted when 0.1 ml of serum was diluted 1:60 with an acidic acetate buffer at pH 4.42 in a low ionic strength (0.01). This turbidity was produced by the separation of certain proteins termed "acid precipitable globulin" (APG). The serum APG level was conveniently quantitated and always represented a major moiety of the total alpha-2 plus beta globulins. APG turbidity was independent of the thymol turbidity value and of the serum concentrations of albumin, mucoprotein or protein-bound polysaccharide. The conversion of APG turbidity units into precise equivalents of alpha-2 plus beta globulin concentration estimated from paper electrophoretic patterns was not feasible because a) the APG turbidity appeared to be suppressed within limits by progressively increasing concentrations of gamma globulin, and b) a wide variation in the lipid-protein ratios of different APG samples was accompanied by a relatively inconstant protein-staining affinity. Despite these factors limiting the quantitative interpretation of APG turbidity values, there was a satisfactory correlation be-



tween the recognition of gross changes in the serum alpha-2 plus beta globulin concentrations on protein-stained paper electrophoretic patterns and the observed serum APG turbidity value, except in sera with marked hyperlipemia.

APG turbidity in normal adult subjects, ages 20-40, varied from 4 to 8 units with mean and standard deviation of  $6.1 \pm 0.6$  and mean variation in replicate samples of 0.3 units. In diverse pathologic sera, APG varied from 2 to 63 units. The ratio of APG turbidity to gamma globulin (zinc sulfate) turbidity, i.e., APG/ZS was employed to supplement the APG turbidity value in providing a broader guide to gross shifts within the globulin spectrum. APG/ZS varied in normals from 0.6 to 1.8 with mean and standard deviation of  $1.06 \pm 0.33$ . A possible clinical significance of observed variation in APG/ZS from 0.03 to 9.6 in sera from diverse pathologic states was suggested.

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## CERVICAL THYMUS GLAND

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Among the developmental abnormalities which may affect the thymus gland is complete or partial failure of its descent in the embryo. According to Patten (1), the thymic primordia in man appear late in the sixth week as ventral out-growths of the third pharyngeal pouches. By the early part of the seventh week, the primordia have considerably elongated but are still connected with the pharyngeal pouches and remain associated with the pair of parathyroid glands derived from the third pharyngeal pouches. During the seventh week, they increase rapidly in mass and their distal tips begin to approach each other as they swing toward the midline just caudal to the thyroid primordium. By the middle of the eighth week the distal tips of the thymic primordia have made contact with each other and have started to descend under the sternum into the mediastinum where they lie in contact with the parietal pericardium. The fusion of the right and left thymic primordia usually remains superficial so that the organ never entirely loses its original paired character.

There have been very few reports of cervical thymus glands. Hyde, Sellers and Owen (2) reported a case of unilateral thymic cyst high in the neck just below the angle of the right mandible and anterior to the sternocleidomastoid muscle. Pre-operatively the cystic mass was considered to be a probable branchiogenic cyst. Arnheim and Gemson (3) reported the first case of persistent cervical thymus gland due to partial failure of descent in an infant in which thymectomy was performed. Gilmour (4) reported post-mortem studies of thirteen cases showing thymic tissue in unusual positions. Eleven of these were infants. One case showed bilateral and another unilateral hypoplasia of the thymus with complete failure of descent from the position in early embryonic life high in the neck. In the case showing unilateral hypoplasia, the other thymus was enlarged and had crossed over into the thorax on the opposite side. Four cases of left-sided partial failure of descent were recorded, two with the thoracic thymus extending high up into the neck and two with an elongated accessory portion of the thymus passing into the neck from a short distance above the upper pole of the main thoracic thymus. There were seven cases in which thymic inclusions were found within the thyroid gland. Reviewing the literature on abnormalities of the thymus Gilmour (4) found post-mortem studies on thirteen additional cases. Five of these revealed partial failure of descent of the thymus. Three showed accessory thymic tissue in the neck. There were two cases of thymic inclusions within the thyroid, two of complete absence of descent of the thymus and one cystic thymus associated with a parathyroid.

Because of the scarcity of reports on the subject and because of the difficulties it

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presents in diagnosis, the following case of cervical thymus due to partial failure of descent is reported.

#### CASE REPORT

R. G., a 21-month-old male child, was admitted to the hospital Oct. 20, 1953 for evaluation of a mass in the neck. His history disclosed the fact that bilateral inguinal hernias were present at birth and were subsequently repaired along with repair of a hydrocele.

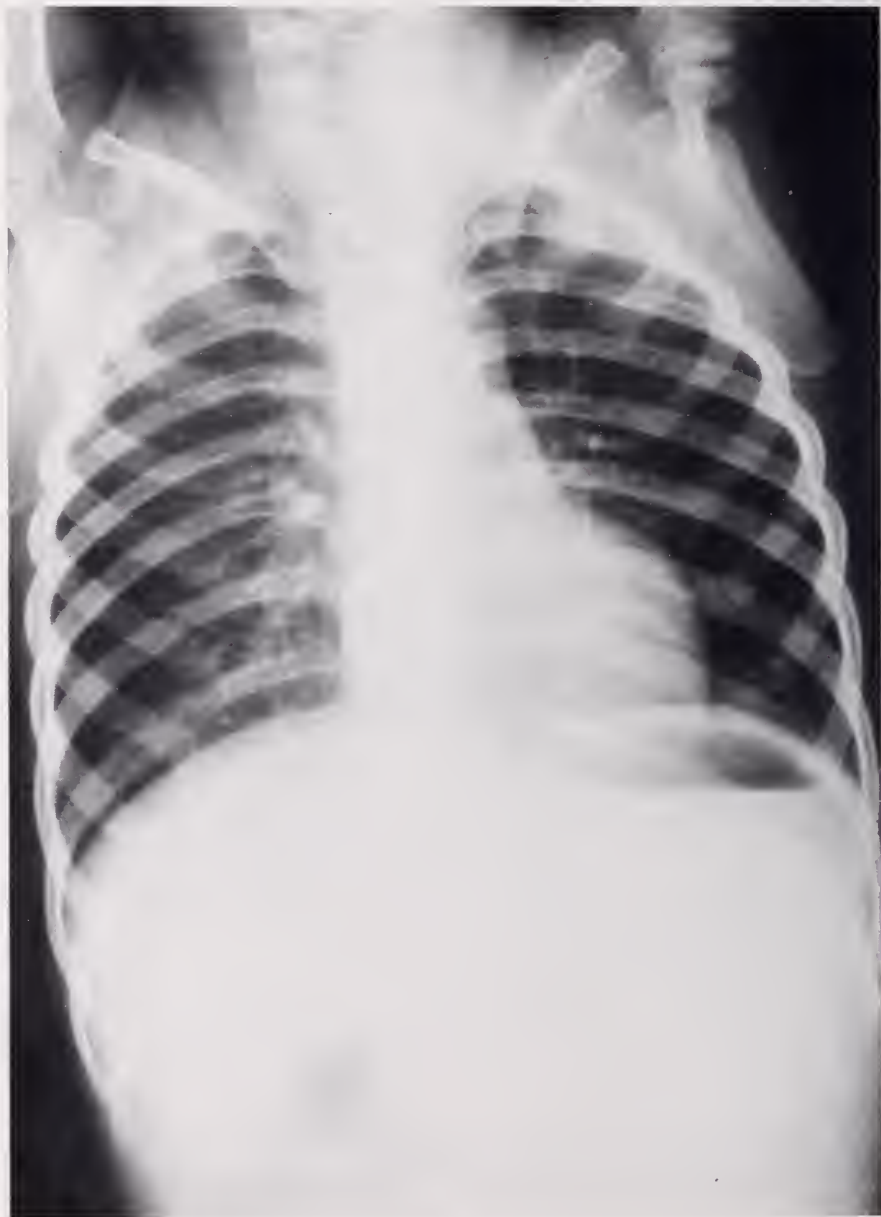


FIG. 1. Examination of the chest made in inspiration shows no abnormalities. There is no evidence of a superior mediastinal mass. The trachea is not displaced.



FIG. 2. Lateral view of the neck at the end of expiration shows a homogeneous soft tissue density just above suprasternal notch. There is no significant compression of trachea.

Physical examination revealed a well nourished infant, about 21-months of age, in no acute distress. The examination was negative except for a soft spongy rounded mass which appeared in the suprasternal fossa when the child strained as in crying or when he was held in the inverted position. The mass was about 4 x 5 cms. in size and could be sharply delineated. It extended slightly to the left of the midline. No bruit could be heard over it. When the child was at rest nothing could be palpated in the neck. There were no swellings or





FIG. 3. Examination made in inspiration fails to demonstrate mass. Note ballooning of pharynx.

masses palpable in either axilla. Two inguinal herniorraphy scars were noted. The testes were normal in size and position. X-ray examination of the chest showed no abnormalities of the heart or lungs. The superior mediastinum was not widened (Fig. 1). Lateral views of the neck at the end of expiration demonstrated a homogeneous soft tissue density in the region of the suprasternal notch. There was no evidence of any air within this density.



FIG. 4. Large bilobed thymus weighing 27 gms. and measuring 12 cm. in length. Microscopic examination revealed only hypertrophied thymic tissue.

There was no evidence of any significant compromise of the tracheal lumen (Fig. 2). On deep inspiration the soft tissue density was not seen (Fig. 3). There was, however, during this phase of respiration, remarkable ballooning of the pharynx. There was no evidence of any calcification in the soft tissues of the neck.

On Oct. 29, 1953 operation was performed under general intratracheal anesthesia. The neck was hyper-extended and a low collar incision made through the platysma. On retraction of the sternothyroid muscle a lobulated, smooth spongy mass was encountered at the level of the suprasternal notch. The mass was delivered from the anterior mediastinum, separated from the dome of the pleura on the left and from the innominate vein and trachea on the posterior surface. The mass proved to be an enlarged thymus and was freed from its fascial attachments and delivered.

Pathological examination of the specimen showed it to consist of an enlarged bilobed thymus weighing 27 gms. and measuring 12 cms. in length. The capsule was thin, smooth and glistening. The parenchyma was a homogeneous, light reddish-brown with a lobulated structure on sectioning. Microscopic examination showed only hypertrophied thymic tissue. There was no evidence of neoplasia (Fig. 4).

#### DISCUSSION

The most common congenital tumefactions occurring in the necks of infants which must be considered in the differential diagnosis of cervical thymus are thyroglossal cyst, branchiogenic cyst and cystic hygroma.

Thyroglossal cysts which arise from the thyroglossal duct are essentially mid-line structures. They may be found at any level between the submental region and the suprasternal notch. Usually they are at about the level of the hyoid bone. They may vary considerably in size and are usually smoothly rounded and have well defined margins. Occasionally a small cyst will lie slightly to one side of the midline. A low lying thyroglossal cyst may be difficult to differentiate from a persistent thymus. In the case reported by Arnheim and Gemson (3) and in the case reported here the ectopic thymus was in the region of the suprasternal notch but varied in size and position with respiration. In addition a mediastinal portion of the thymus was demonstrated by x-ray in the former case.

Branchiogenic cysts occur in the anterior triangle of the neck always in front of the sternocleidomastoid muscle. They may occur anywhere along the anterior border of this muscle from the manubrium to the angle of the jaw. While this type of congenital cyst should not offer great difficulty in differentiation from the type of undescended thymus reported here and by Arnheim and Gemson (3), it is to be noted that the thymic cyst reported by Hyde, Sellers and Owen (2) was found just below the angle of the right mandible and anterior to the sternocleidomastoid muscle and was indeed diagnosed as a branchiogenic cyst previous to operation.

Cystic hygromas are endothelium-lined, fluid containing cysts of lymphatic origin (5). They may occur in the neck, axilla, chest wall or groin. According to Gross (5), about four-fifths of all hygromas occur in the neck. When they do, they are most apt to lie in the posterior triangle, behind the sternocleidomastoid muscle, often occupying the supraclavicular fossa or extending over toward the shoulder. Occasionally such a cyst may lie in the anterior triangle. When this occurs the cyst is usually situated high in the neck and may override the mandible. Some hygromas are dumbbell-shaped, the upper portion extending into the

neck, the lower portion lying in the thorax. In these cases, there may be changes in the size of the cervical portion with changes in the intrathoracic pressure. Straining, crying and coughing may result in an increase in the size of the cervical component. These cysts palpated in the neck are usually not very tense and do not have very well defined borders.

The case presented here apparently represents the combination of incomplete descent and hypertrophy of the thymus gland. Clinically the child presented the bizarre finding of a suprasternal mass which appeared only when the intrathoracic pressure was increased or the child inverted. During quiet respiration or on deep inspiration the mass could not be palpated in the neck nor demonstrated in the superior mediastinum on roentgen examination. The possibility that this mass was vascular in nature and emptied itself of blood during inspiration was considered. Also entertained, was the possibility of a soft mass which when present in the superior mediastinum simply failed to increase the lateral dimensions of the mediastinum significantly and which was displaced into the lower neck when the intrathoracic pressure was increased. This latter possibility proved to be correct.

The indication for operative intervention in this case was the presence of a tumor in the suprasternal fossa of undetermined nature. If it were possible to make a clinical diagnosis of hypertrophied cervical thymus the question as to whether this constitutes an indication for resection would no doubt arise and would depend largely on the presence or absence of symptoms and on their severity. If the diagnosis is made during exploration, resection, at least partial in nature, appears reasonable. No conclusive evidence has been presented to-date that thymectomy produces any significant effect upon the growth and development of the infant (3).

#### SUMMARY

1. A case of partial failure of descent of the thymus gland in a 21-month-old child is reported.
2. The gland was hypertrophied and appeared in the suprasternal fossa when the intrathoracic pressure was increased or the child inverted.
3. The congenital tumefactions most commonly found in the necks of infants and children are briefly reviewed.

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# METHOD FOR THE DETERMINATION OF RADIOIODINE LEVELS IN BLOOD PLASMA<sup>1, 2</sup>

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Our reports in 1951 and 1952 regarding the value of determinations of the blood levels of radioactive iodine (I-131) after tracer doses in the diagnosis of hyperthyroidism have been followed by wide acceptance of this procedure. Technical improvements, particularly the introduction of the well-type scintillation counter, have greatly simplified the method and allowed the use of even smaller tracer doses than we originally recommended. We have received many inquiries regarding the exact methods now in use and we thought it advisable to describe the procedure in detail so that it could be followed without difficulty and that reproducible results could be obtained.

The purpose of the method is the determination of the concentration of I-131 in the plasma 3 days after a tracer dose. This concentration is expressed in percent of the administered dose per liter of plasma. This has two components: inorganic and protein-bound I-131 and only the protein-bound component has diagnostic significance. In our experience protein-bound I-131 levels greater than 0.26% indicate hyperthyroidism. When both components are less than this critical value no separate determination of the protein-bound component is necessary. When, however, the total concentration exceeds 0.26% it is necessary to determine what fraction of this activity is in the protein-bound component.

## MATERIALS

1. Radioactive iodine: carrier-free I-131 as obtained from the U. S. Atomic Energy Commission or from Abbott Laboratories, Division of Radioactive Chemicals, is used for the tracer dose and for the standards. For the preparation of standards this material is diluted in water (carrier iodide, alkali and sodium bisulfite have not been found necessary) so that 1 ml. of the final solution contains 0.0001, 0.0002, 0.0003, etc. millicuries of I-131.

2. Well-type scintillation counter: Standard counters of this type may be used which have a diameter of about 2 inches and are about 2 inches long. The well should be of such size that a 4 ml. sample of liquid in the test tube is completely contained within the well, and that the well accepts test tubes described under 3. Any suitable scaling system may be used.

3. Test tubes: Pyrex test tubes 15 x 125 mm. (15 ml. volume)

4. 10 per cent trichloroacetic acid.

5. 2 molar sodium carbonate or sodium hydroxide.

6. 1 mm. diameter glass stirring rods 150 mm. long or common applicator sticks of the same length.

<sup>1</sup> From The Andre Meyer Department of Physics, The Mount Sinai Hospital, New York City.

<sup>2</sup> I-131 supplied on allocation by the United States Atomic Energy Commission.

Important precaution—all the glassware, syringes, needles, test tubes and pipettes used should be reserved solely for this determination. If they are used for tracer or therapeutic concentrations of I-131 the decontamination problem becomes almost insuperable. The hands of the worker should be carefully washed before touching any of the glassware used. Minimal contamination of glassware or the crystal and its enclosure will result in serious errors.

#### PROCEDURE

Twenty-five to 100 microcuries of I-131 are administered by mouth in about 100 ml. of water and the exact dose recorded. This tracer dose may also be given parenterally but it is not necessary for this test. The thyroidal uptake, the urinary excretion or both, may be determined in the usual manner. Seventy-two hours after the tracer dose, 10 ml. of blood are drawn by venipuncture. Oxalate is added to prevent coagulation. The 72 hour period is not critical, but it is preferable not to draw blood before 48 or after 96 hours. The blood is centrifuged and 4 ml. of plasma are pipetted into a 15 x 125 mm. test tube. The outside of the tube is carefully dried and the tube is placed in the well of the scintillation counter and its radioactivity measured.

With the counting set-up used in this laboratory a 4 ml. sample containing 0.001 microcuries I-131 gives 18 counts per second; the background count is 4 to 5 counts per second. The sensitivity required in the radioactivity measurements is such that it should be possible to determine a protein-bound I-131 (PBI-131) of 0.1 per cent with a precision of 10 per cent of this value. If a tracer dose of 25 microcuries is used, then in 4 ml. blood of a patient with 0.1 per cent PBI there will be present 0.0001 microcuries I-131 which will give a net counting rate of about 2 counts per second. Under these conditions a determination can be done with a 10 per cent precision in 10 minutes overall counting time (about 5 minutes counting for sample and background each). If a larger tracer dose is given, either the counting time can be reduced (to about  $1\frac{1}{2}$  minutes with a 100 microcurie tracer dose) or a smaller blood sample than 4 cc. can be used.

Correction is made for decay from the time of administration of the tracer to the time of measurement, usually three days. If the activity in the 4 ml. plasma sample is less than 0.001 per cent of the administered dose, or 0.26 per cent per liter, no further manipulation is required; this value is not in the hyperthyroid range.

If the sample has a concentration in excess of 0.26 per cent of the administered dose per liter it is necessary to determine the PBI-131. In order to do this, we add to the 4 ml. sample in the same test tube previously measured, 10 ml. of 10 per cent trichloroacetic acid. A glass stirring rod or a wooden applicator stick is used to insure complete mixing. This is allowed to remain in the test tube throughout the rest of the procedure. After thorough mixing the tube is centrifuged at 3000 to 3500 revolutions per minute for five minutes. This results in a clear supernatant fluid and a firmly packed precipitate. The supernatant fluid is decanted off and 10 ml. of water and a few drops of the trichloroacetic acid are added. Using the same glass rod, the precipitate is thoroughly mixed with the

water making certain that no particles of precipitate remain unwashed in the bottom of the tube. The tube, still containing the glass rod, is again centrifuged. The supernatant fluid is decanted as before and one more washing is carried out as above. This final supernatant is again decanted off leaving only the precipitate and the glass rod in the tube. Then 2 M. sodium carbonate (or hydroxide) is added to dissolve the precipitate to a final volume of 4 ml. The outside of the tube is carefully wiped and the radioactivity measured as before in the well counter. Values above 0.27 per cent of the administered dose per liter are considered indicative of hyperthyroidism. The washing procedures here described will remove all inorganic I-131 likely to be encountered and the values obtained after washing represent only protein-bound iodine 131.

An analysis of a group of patients composed of 400 euthyroids and 100 hyperthyroids has shown that by the use of the method described here a correct diagnosis could be made in 98.5 per cent of the total.

## PNEUMOENCEPHALOGRAPHY WITH MINIMAL WITHDRAWAL OF CEREBROSPINAL FLUID\*

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After lumbar puncture, patients commonly complain of headache, which sometimes may be quite severe. Such a procedure requires no injection of air; there is only the withdrawal of fluid. Since in performing a pneumoencephalogram more cerebrospinal fluid is removed than during the usual lumbar puncture, it was felt that the discomfort following pneumoencephalography might in part be referable to the removal of fluid rather than to the usually emphasized factor of the quantity of air injected.

Severe discomfort following pneumoencephalography may last several days. It may include headache, nausea, vomiting, sweating, and involuntary defecation and urination. Patients also have experienced chilliness, hiccough, anorexia, backpain, seizures, dizziness, tinnitus, stiff neck, hyperesthesia of the skin, and syncope. Cyanosis, pallor, eyeball protrusion, distention of scalp veins, fever, decrease in temperature, positive Kernig sign, and confusion have been observed (1). Death has occurred after pneumoencephalography.

Classically, pneumoencephalography has been performed by the removal of cerebrospinal fluid in an attempt to "compensate" for the addition of air into the ventricular system. Thus in 1918, Dandy (2) stated that "it is necessary to remove at least more cerebrospinal fluid than the contents of one ventricle and to replace this fluid with an equal quantity of air. . . . If the air injected is greater in volume than the fluid withdrawn, acute pressure symptoms will result." A year later he discussed a method of visualizing the subarachnoid space (3) in which "a small quantity of spinal fluid is withdrawn and an equal amount of air injected into the spinal canal. This process of substitution is repeated until the fluid ceases to appear on aspiration." Gardner and Nichols (4) in 1933 reported that ". . . after the cerebrospinal fluid has once been removed, it reaccumulates more rapidly. Therefore, if the fluid pressure was high before the procedure, it may reach a dangerous level a few hours later unless the lesion is removed or a decompression is provided." In their technique, using the lumbar route, ". . . the fluid is then removed in 5 cc amounts and air substituted in similar amounts until no more fluid can be obtained." In his monograph, "Encephalography", Robertson (5) states that "Alternate introduction of air and removal of fluid is continued until a satisfactory filling is seen." Lindgren (6) performed lumbar pneumoencephalography with removal of variable amounts of cerebrospinal fluid except in cases of increased intracranial pressure, wherein he employed cisternal encephalography. The technique of Davidoff and Dyke (7) included "removing an initial quantity of 10 cc of

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cerebrospinal fluid and replacing it with only 5 cc of gas. Thereafter, 5 cc of fluid and 5 cc of gas are alternately removed and injected." Falk (8) writes that "less fluid is always removed than air injected." Shapiro and Robinson (9) outlined a method whereby "The transient rise in pressure was corrected by drainage of cerebrospinal fluid under manometric control so that the spinal pressure was restored to its pre-injection level, and similarly corrected following each subsequent incremental air injection."

This report concerns a new pneumoencephalographic technique. No cerebrospinal fluid is removed except for those drops lost inadvertently during the procedure or a small quantity (not more than 5 cc) necessary for the performance of laboratory tests.

#### TECHNIQUE

Routinely, each patient receives phenobarbital 300 mgm and atropine (or scopolamine) 0.4 mgm hypodermically one hour before pneumoencephalography. (The dosage was altered in the cases of two infants and a 10½ year old girl and no medication was given to two almost comatose patients.)

The patient is seated and a lumbar puncture is performed using a #18 needle. If possible, no cerebrospinal fluid is withdrawn. X-rays are taken after 8 to 10 cc of air are injected to visualize the 4th ventricle, aqueduct of Sylvius and 3rd ventricle. If cerebrospinal fluid (not more than 5 cc) must be removed, it is done after these films are taken. Additional air then is injected for study of the remainder of the ventricular-subarachnoid system. The amount of additional air is determined by means of scout films taken with the patient in the erect position. In taking the x-rays, the patients are placed in the positions suggested by Lindgren (10) and Robertson (5).

Following pneumoencephalography the patient is placed in bed and the following medications are administered (if needed) for headache: caffeine-phenacetine-aspirin tablets; caffeine sodium benzoate, 0.5 Gm—intramuscularly.

Of 35 cases studied, 30 had a total injection of air ranging from 25 to 80 cc. An additional 5 cases are cited in which studies were limited to the 4th ventricle, aqueduct of Sylvius and 3rd ventricle. Thirteen patients had no cerebrospinal fluid withdrawn; twenty-two patients had 5 cc or less withdrawn for testing. Patients studied were in an age range of from 3½ months to 73 years and included individuals diagnosed on admission as having a brain tumor, convulsive disorder, encephalopathy, and hydrocephalus.

#### RESULTS

During the procedure, 27 patients had headache, 7 had either nausea, retching or vomiting, 1 had paresthesias, 1 had marked sweating, 1 had a generalized seizure, and 1 had a focal seizure.

*One to two hours after pneumoencephalography:* Of 27 headaches (20 of which were classified as severe), 4 had decreased to moderate, 8 had decreased to slight, and 4 had disappeared. Four patients had either nausea or vomiting.

TABLE 1

*Type and Duration of Reactions following Pneumoencephalography*

Patient No.	Cc CSF Out	Cc Air In	Type Of PEG	Admission Diagnosis	Condition during PEG	Condition after PEG
1	5	70	Complete	Convulsive disorder	Severe headache, marked sweating	Slight headache after 3-6 hours; no complaints after 7 hours
2	5	50	Complete	Brain tumor (posterior fossa)	Severe headache	Moderate headache after 1-2 hours; slight headache after 3-6 hours
3	0	60	Complete	Brain tumor (supratentorial)	Severe headache	No headache after 18 hours
4	4	60	Complete	Brain tumor (supratentorial)	Severe headache	No headache after 3-6 hours; slight headache after 20 hours
5	0	25	Complete	Brain tumor (supratentorial)	Severe headache, vomiting, focal seizure	Slight headache after 1-2 hours
6	0	20	IV ventricle	Brain tumor (posterior fossa)	Moderate headache	No headache after 9-10 hours
7	0	45	Complete	Convulsive disorder	Severe headache, vomiting	Moderate headache after 1-2 hours
8	0	25	Complete	Convulsive disorder	Severe headache, vomiting	Very slight headache after 1-2 hours
9	0	40	Complete	Brain tumor (supratentorial)	Severe headache, retching	Slight headache after 1-2 hours; no headache after 3-6 hours
10	0	70	Complete	Brain tumor (supratentorial)	Severe headache, vomiting, numbness of right hand	Slight headache, vomited after 1-2 hours
11	0	60	Complete	Brain tumor (supratentorial)	Severe headache	No headache after 3-6 hours
12	2	45	Complete	Brain tumor (supratentorial)	Slight headache	No headache after 1-2 hours
13	0	40	Complete	Hydrocephalus	Well tolerated	No change
14 (Infant)	4	28	Complete	Convulsive disorder	Cried	Asleep after 1-2 hours
15 (Infant)	3	60	Complete	Convulsive disorder	Severe headache, retching	No headache after 3-6 hours
16	0	80	Complete	Brain tumor (chiasm)	Severe headache	Slight headache after 1-2 hours; no headache after 3-6 hours
17	0	10	III, IV ventricles	Brain tumor (posterior fossa)	No discomfort	Same
18	0	16	III, IV ventricles	Brain tumor (posterior fossa)	No headache	Same
19	2	40	Complete	Brain tumor (chiasm)	Severe headache	Slight headache after 3-6 hours; slight headache after 20 hours
20	3	18	IV ventricle	Brain tumor (posterior fossa)	No apparent reaction	Same
21	5	50	Complete	Brain tumor (supratentorial)	Moderate headache	No headache after 1-2 hours; syncope after 12 hours
22	0	10	III, IV ventricles	Encephalopathy involving brainstem	Slight headache	No headache after 1-2 hours
23	5	58	Complete	Brain tumor (supratentorial)	Severe headache; generalized seizure	Moderate headache, nausea after 1-2 hours; no headache, slight nausea after 7 hours

TABLE I—*Continued*

Patient No.	Cc CSF Out	Cc Air In	Type Of PEG	Admission Diagnosis	Condition during PEG	Condition after PEG
24	3	60	Complete	Brain tumor (supra-tentorial)	Very slight headache	Right-sided seizure after 3-6 hours; more alert than pre-PEG after 20 hours
25	4	40	Complete	Encephalopathy	Moderate headache	Slight headache after 1-2 hours; no headache after 7 hours
26	5	30	Complete	Convulsive disorder	Severe headache	Slight headache, vomiting, after 1-2 hours; slight headache after 3-6 hours
27	5	70	Complete	Brain tumor (supra-tentorial)	Severe headache	Severe headache lasted 24 hours
28	3	50	Complete	Brain tumor (supra-tentorial)	Severe headache	Severe headache lasted 10 hours
29	2	60	Complete	Convulsive disorder	Severe headache	Severe headache lasted 20 hours, transient disorientation for place
30	5	45	Complete	Convulsive disorder	Severe headache, nausea	Slight headache after 1-2 hours; no headache after 3-6 hours
31	5	50	Complete	Brain tumor (supra-tentorial)	Severe headache	Moderate headache, nausea after 1-2 hours; no discomfort after 3-6 hours
32	3	50	Complete	Brain tumor (supra-tentorial)	No headache	Same
33	4	48	Complete	Encephalopathy	Moderate increase in pre-PEG headache	No change after 6 hours; same as pre-PEG after 24 hours
34	4	28	Complete	Brain tumor (supra-tentorial)	Moderate headache	Minimal headache after 24 hours
35	2-3	28	Complete	Brain tumor (supra-tentorial)	No discomfort	Transient pain at back and thighs after 3 hours; responded to suggestion

*Three to six hours after pneumoencephalography:* Further reduction of symptoms had occurred, including disappearance of 7 more headaches. One patient continued to have nausea. Three patients who had previously had either nausea or vomiting now had neither. Three other patients began to have nausea or vomiting. One patient who had no seizures during the procedure had a right-sided seizure.

*Seven hours after pneumoencephalography:* Only 4 severe headaches remained; 1 of these lasted a total of 10 hours, 1 lasted 20 hours and 1 lasted 24 hours. One patient got out of bed and experienced syncope, 1 had transient disorientation for place, and 1 said later that she had had nightmares. Of patients with previous nausea, vomiting or retching, only slight nausea persisted at 7 hours (1 patient). No other patients developed nausea, vomiting or retching.

Reactions (and their duration) of the individual patients are presented in Table I. The longest period of severe discomfort following pneumoencephalography was 24 hours (Headache—1 patient). It is to be noted that each of the 3 patients who had either seizure or syncope during or after pneumoencephalography had also had seizures before pneumoencephalography.

Of the pneumoencephalograms obtained by this technique, 8 were considered

TABLE II  
*Validity of Radiographic Results*

Admission Diagnosis	No.	PEG Interpretation		Surgical Confirmation
		Positive	Negative	
Brain tumor				
Posterior fossa.....	6	1	5	1
Chiasmal region.....	2	2	0	No operations
Other supratentorial tumors.....	15	5	10	3. No operations on other 2 pneumoencephalogram- positive cases
Total.....	23	8	15	4
Convulsive disorder.....	8	All 8 pneumoencephalograms normal		
Encephalopathy.....	3	All 3 pneumoencephalograms showed gen- eralized dilatation of the ventricular system		
Hydrocephalus.....	1	Generalized dilatation		

positive for brain tumors. Of these 8 patients, 4 were operated upon and were found to have a brain tumor. The 8 patients with the admission diagnoses of convulsive disorder all had normal pneumoencephalograms. The 3 patients with the admission diagnoses of encephalopathy all had pneumoencephalograms which showed generalized dilatation of the ventricular system. The one patient with the admission diagnosis of hydrocephalus had a pneumoencephalogram which showed generalized dilatation of the ventricular system. The remaining 15 patients who had admission diagnoses of brain tumor had pneumoencephalograms which were considered to be normal or showed generalized dilatation of the ventricular system (Table II).

#### DISCUSSION

As previously noted, more time honored methods of pneumoencephalography are often followed by prolonged morbidity and even an occasional mortality. These undesirable concomitants are certainly hardly obviated by ventriculography since damage peculiar to ventriculography alone, such as hemorrhagic needle tracts into vital areas (eg., the internal capsule), have been seen by the authors and described by others. Lindgren (10) has graphically shown a marked trend away from ventriculography and toward pneumoencephalography. This trend toward pneumoencephalography is inclusive of cases in which posterior fossa neoplasm is suspected and subsequently proven as well as cases of increased intracranial pressure due to neoplasms situated in any other part of the brain. Furthermore, from the radiographic standpoint, the pneumoencephalographic demonstration of the subarachnoid-ventricular system by the method of pneumoencephalography herein described is as adequate as, and sometimes superior to, that of ventriculography.

We return now to consideration of the condition of the patient as regards



comparative discomfort and safety of the various air encephalographic procedures with which this paper is primarily concerned. Attestation from other sources of the relative safety of the subarachnoid injection of gas is obtained from the work of Brage (11, 12). In his department, rapid injection of 100 to 150 cc of gas (carbogen) into the subarachnoid space of psychotic patients has been performed therapeutically for several years. He states that during the procedure he is prepared to do artificial respiration in the event that it is necessary but adds that this has never happened. In his technique, cerebrospinal fluid may be either withdrawn in varying quantities or not at all, depending on the type of "Diencefaloshock" desired. Cerebral pneumotherapy, first used by Foerster (13) in 1924 for post-traumatic complaints is used by Delay et al (14), for cases of mental illness and certain metabolic diseases (these workers, however, use air-fluid replacement techniques).

For initial films of only the 3rd and 4th ventricles and the aqueduct of Sylvius, it is not unusual to inject a small amount of air without withdrawing fluid. However those using this method customarily withdraw cerebrospinal fluid before injecting additional air. Guiral (15) in performing pneumoencephalography emphasizes the use of small amounts of air as introduced to his department by Negrin (16). In films of the 3rd and 4th ventricles and aqueduct of Sylvius he does not withdraw cerebrospinal fluid and sometimes continues thus for the remainder of the pneumoencephalogram. Lindgren (17) emphasizes the careful radiographic utilization of each small increment of air injected. He mentions "fluid-air exchange" and withdraws cerebrospinal fluid except that he feels that if there is increased intracranial pressure, it may be safer to not withdraw cerebrospinal fluid.

In this study, all pneumoencephalograms, complete or partial (those in which interest was limited to 3rd and 4th ventricles and aqueduct alone), were done with minimal or non-withdrawal of cerebrospinal fluid. The study includes patients with papilledema, increased cerebrospinal fluid pressure, and diagnoses of "tumor suspect" (some proven) in various parts of the brain including the posterior fossa. In this admittedly small preliminary series of 35 patients there have been no deaths and the longest period of severe discomfort following pneumoencephalography was 24 hours (headache—1 patient).

#### SUMMARY

Pneumoencephalographic studies were performed on 35 patients using a new method, viz., injection of air and withdrawal of 0-5 cc of cerebrospinal fluid. The procedure as described is simple and the resultant X-rays show the desired filling of the subarachnoid-ventricular system. This study includes patients with papilledema, increased cerebrospinal fluid pressure, and brain tumors in various parts of the brain including the posterior fossa (4 tumors verified by pneumoencephalography and by surgery and 4 additional tumors substantiated by pneumoencephalography but which did not come to surgery). In comparison with the usual methods of pneumoencephalography employing withdrawal of much larger amounts of cerebrospinal fluid, it has been the impression of the

physicians and nurses that in those patients in whom this new method was used, there was a marked reduction in the duration of discomfort following pneumoencephalography. We are attempting to substantiate this with controlled studies now in progress.

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## OCCLUSION OF THE MESENTERIC ARTERIES AND VEINS WITH INFARCTION OF THE BOWEL

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### INTRODUCTION

Recognition of the pathologic picture of bowel infarction due to mesenteric vascular occlusion dates back to the initial descriptions of Tiedmann (1) and of Virchow (2). Half a century later, in 1895, Elliot's report (3) of the first successful resection for this condition initiated clinical interest, and his lucid analysis of the etiologic mechanisms stands in its essentials to the present day. He pointed out that hemorrhagic infarction may be due to either arterial or venous occlusion. Patients with arterial mesenteric occlusion usually had as a background heart disease or arteriosclerosis, while patients with venous occlusion often were found to have cirrhosis of the liver, phlebitis, or idiopathic thrombotic states. Elliot's successful case was one of idiopathic venous thrombosis in a twenty-five year old male and a fatal one was due to arterial occlusion in a man of seventy. Immediate resection and anastomosis was advocated as the procedure of choice whenever possible. He thought that surgical successes could be anticipated chiefly in the venous group with purely local lesions.

For this report the clinical material from the records of the Mount Sinai Hospital\* has been reviewed in order to help clarify the clinical picture and to stimulate early diagnosis and aggressive therapy. Only cases proved by operation, autopsy, or both are included.

### MECHANISM OF INTESTINAL INFARCTION

At the outset it must be emphasized that the common result of either arterial or venous occlusion is hemorrhagic infarction. In the case of venous block the origin of the dark reddish-black engorged bowel wall and thickened edematous mesentery is readily understood—continued influx under systemic arterial pressure of blood which cannot escape from obstructed veins, which become engorged, causing interference with intrinsic bowel wall circulation, extravasation of blood into the tissues, anoxia, necrosis, bacterial invasion from the lumen through the devitalized gut and peritonitis with or without gross perforation. In addition, a considerable volume of blood is lost from the vascular bed into the bowel wall, into the lumen, the mesentery, and the peritoneal cavity so that shock results from the fluid loss as well as in association with peritonitis. This is of course the usual mechanism of intestinal infarction in mechanical intestinal obstruction, whether in strangulated hernia, band obstruction, volvulus or intussusception—states which are not considered in this paper.

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\* Included in this series are two cases who were treated at Doctors Hospital, N. Y. which the writer had the opportunity to observe.



Arterial occlusion also produces hemorrhagic infarction but through a somewhat different train of events. Klein (4) pointed out that ligation of the superior mesenteric artery in the dog produced violent tetanic contractions and marked anemia of the bowel wall lasting two to three hours followed by a state of relaxation accompanied by marked congestion. The bowel wall and mesenteric veins became filled with blood flowing retrograde from other areas of higher pressure. Secondary venous thrombosis due to stasis often supervened. Moore (5) mentions that only about 2 per cent of the cases of arterial mesenteric block remain as anemic infarcts, the rest becoming hemorrhagic. The ultimate state of affairs leading to gangrene progresses more quickly in the arterial occlusions and undoubtedly contributes to the more acute clinical picture and desperate prognosis.

Certain functional changes occur in both types of hemorrhagic infarct which lead to further deterioration. It may be that collateral vascular spasm causes interference with blood flow beyond the actual anatomical distribution of the blocked vessel causing extension of the infarcted area. This may be reversible as exemplified by two cases described by Orr, Lorhan, and Kaul (6). These authors showed that splanchnic nerve block led to regression from a hopeless situation to a resectable and curable one in one case and to complete recovery without the necessity for resection in another. The other non-organic feature of considerable importance is the status of the general circulation. Shock is a common accompaniment of bowel infarction acting through three possible mechanisms: 1) neurogenic, due to the severe pain of sudden occlusion; 2) secondary to massive blood and fluid loss into the bowel wall, lumen, and peritoneal cavity; and 3) as a result of peritonitis. Shock may also antedate the intestinal infarct if it has occurred in the course of an acute myocardial infarction or cardiac arrhythmia, either one of which may be responsible for the release of an embolus into the arterial circulation as the proximate cause of the mesenteric occlusion. Indeed Klein (4) described instances of recent intestinal infarctions in patients with old occlusions of the superior mesenteric artery in which gangrene ensued as the result of vascular collapse without any new arterial injury.

#### ANATOMICAL FACTORS

The arterial supply of the abdominal portion of the gastrointestinal tract arises from three main vessels: 1) celiac axis, 2) superior mesenteric artery, and 3) inferior mesenteric artery. All are branches of the abdominal aorta. Infarction of the bowel is limited in most instances to the distribution of the superior mesenteric artery. The anatomical factors to be mentioned appear to play a role in this peculiarity.

1) Celiac axis: This vessel passes nearly horizontally forward dividing promptly into three main branches—the hepatic, the left gastric, and the splenic. All three contribute to the arterial supply of the stomach. Rich intramural anastomoses render this organ almost immune to infarction. A collateral supply with the superior mesenteric exists via the anastomoses between the superior pancreaticoduodenal and the inferior pancreaticoduodenal, a small vessel which arises from the main trunk or the first intestinal branch of the superior mesenteric

artery. The right angle that the celiac axis makes with the aortic stream mitigates against embolism to this vessel as opposed to the obtuse angle between the aorta and the superior mesenteric artery which favors embolic occlusion of that vessel.

2) Superior mesenteric artery: This trunk supplies the entire jejunum and ileum and the right colon around to the mid-transverse. It takes origin from the aorta about 1.25 centimeters below the celiac and as it passes downward forms an obtuse angle with the aorta. Its meagre anastomosis with the celiac axis above and an almost equally inadequate collateral with the inferior mesenteric (via the marginal artery connecting the middle colic and the left colic) makes this vessel in effect an end-artery so that when the main trunk of the superior mesenteric artery has been occluded the entire small intestine and the right colon may be unable to survive. The varying caliber of the marginal artery is responsible for the varying involvement of the ascending colon, hepatic flexure and transverse colon when the superior mesenteric has been blocked.

In contradistinction to the above the branches of the superior mesenteric artery anastomose freely with each other in the mesenteric arcades. Experimental work by Noer and Derr (7) and diagrams in the papers of Johnson and Baggenstoss (8) indicate the mechanism of arterial vascular occlusion without infarction. If the superior mesenteric artery is intact, infarction occurs only when the vessels immediately adjacent to the bowel wall (vasa recta) become occluded. This arrangement of the collateral circulation explains situations in which there is an old organized thrombus in the superior mesenteric trunk and a recent thrombus further distal with infarction of only a small portion of the bowel, or such a case as occurred in this series in which an embolus to a cecal artery caused a localized infarct. Undoubtedly many emboli must lodge in the larger intestinal branches without ever causing clinical symptoms. On the other hand, collateral vascular spasm can be great enough to cause infarction beyond the distribution of the occluded vessel. The reversibility of this latter situation has been referred to previously (6).

3) Inferior mesenteric artery: This vessel is a smaller trunk than either of the two previous ones, and presents no obvious anatomical peculiarities other than its small size and its fairly good collateral anastomoses with the superior mesenteric above (via the middle colic) and the middle hemorrhoidal below. Gangrene as a result of involvement of this vessel in an occlusive process practically always occurs in conjunction with block of the superior mesenteric as well. Its division in association with resection of lumbar aortic aneurysm causes no difficulty, although collateral circulation may have developed in this instance.

The abdominal aorta is commonly affected by atherosclerosis in older individuals. There is usually a sharp dividing line between the relatively slight changes in the thoracic aorta and the advanced disease which begins at the level of the diaphragm. Atheromatous plaques, ulceration, thromboses, and aneurysms occur and extend into the mouths of the principal gastro-intestinal branches of the aorta.

The venous drainage of the gastro-intestinal tract parallels the arterial supply as far as the pattern of intestinal distribution is concerned. The inferior mes-

enteric vein enters the splenic behind the body of the pancreas or may occasionally enter a confluence of the splenic and superior mesenteric. Centrally the superior mesenteric joins the splenic behind the neck of the pancreas to form the portal vein. Anatomical factors do not appear to be as important in occlusions of the venous system as they are in the arterial channels. However embryological features such as spread of infection along the umbilical vein and thence into the portal must not be forgotten for this may account for certain cases of cavernomatous transformation of the portal vein with manifestations in later life such as mesenteric venous thrombosis.

#### MATERIAL

A total of forty-seven cases of mesenteric vascular occlusion, all proved by operation, autopsy, or both were available for study. Forty-four of these had intestinal infarction while three (in the venous group) had venous thrombosis without bowel compromise. Separate consideration of the cases of arterial and venous occlusion is essential to a comprehension of the clinical picture, mechanisms, and prognosis despite the fact that hemorrhagic bowel infarction is the common denominator in both types of lesion. Elliot (3) first pointed out this distinction, and more recent authors—Berry and Bougas (9), Brown (10), Donaldson and Stout (11), Dunphy and Whitfield (12), Johnson and Baggenstoss (8), Laufman and Scheinberg (13), Moore (5), Mersheimer, Winfield, and Fankhauser (14), Warren and Eberhard (15), and Whittaker and Pemberton (16)—constantly re-emphasize the importance of distinguishing the two types of vascular occlusion.

#### THE CLINICAL PICTURE

Of the forty-seven cases reviewed, twenty-seven fell into the arterial group while twenty were of the venous variety. The venous type occurs in a much younger age group (average age forty-six as compared to almost sixty in the arterial). The opportunities for operative attack are greater in the venous cases and the only recoveries in this series occurred here as well (Table I). No significant sex differential is noted.

In the arterial category the onset of symptoms is acute, frequently explosive in intensity, and the clinical picture is very often unmistakable. Sixteen of the

TABLE I  
*Mesenteric vascular occlusion—general information*

	Arterial	Venous
Number . . . . .	27	20 (17 infarctions)
Sex . . . . .	M—14, F—13	M—14, F—6
Age (average) . . . . .	59.5 yrs.	46 yrs.
Operations . . . . .	7	11
Resections . . . . .	2	10
Recoveries . . . . .	0	6 (of 10 resections)
Mortality . . . . .	100%	40% (of 10 resections)

twenty-seven patients lived only two days or less, and many of these were admitted to the hospital in shock. Abdominal pain, tenderness, and distention are commonly present. A correct diagnosis is frequently made and in the differential diagnosis, intestinal obstruction and perforated viscus are also commonly considered. All of these are situations which demand prompt operative attention. However shock supervenes rapidly if it has not occurred initially and is so severe that even contemplated surgical attack often cannot be carried out.

In the venous group, thirteen of the twenty patients had symptoms lasting three days or longer. Six were ill over two weeks and three of these are numbered among the six recoveries. The clinical picture is less sharply defined although pain, distention, tenderness, spasm, vomiting, constipation, and shock are frequently seen. It is the slow evolution of the clinical picture, and the comparative mildness of the symptoms when they do occur that leads to difficulty in the differential diagnosis. In one patient such things as perisplenitis, cirrhosis, splenic vein thrombosis, acute pancreatitis, non-icteric hepatitis, incarcerated umbilical hernia, perforated duodenal ulcer (walled-off), and hernia of the fossa of Treitz were all mentioned (Table II).

Anatomical distribution of the infarcted bowel also follows a pattern characteristic of the type of vascular involvement. With arterial block, the distal small bowel, the entire small bowel, and the small and large bowel suffer infarction in increasing order of incidence. The reverse is noted in the group with venous blockade—here the proximal and mid small bowel are most commonly affected while colonic involvement did not occur. The arterial type follows a more central type of pattern with the superior mesenteric artery as the hub, while the venous group reflects a more patchy peripheral involvement. The preponderance of colonic involvement in the arterial occlusions is another factor that may well

TABLE II

*Mesenteric vascular occlusion—symptoms and signs of bowel infarction*

	Arterial (27)	Venous (17)
Duration		
2 days or less.....	16	4 (3 recoveries)
Over 2 days.....	11	13 (3/6 over 2 wks. recovered)
Abdominal pain.....	27	17
Distention.....	14	8
Tenderness.....	18	9
Spasm.....	7	4
Vomiting.....	7 (4 guaiac+)	2 (both guaiac+)
Constipation.....	1	2
Shock.....	10	3
Mass.....	2	2
Ascites.....	0	4
Bloody stools.....	3	1
WBC (over 18,000).....	10	10
Fever (102° plus).....	6	7



TABLE III  
*Mesenteric vascular occlusion—segments of bowel infarcted*

	Arterial (27)	Venous (17)
Jejunum alone	0	3
Ileum alone	5	8
Jejunum and ileum	4	4
Undetermined (sm. int.)	0	2
Duodenum, small and large	1	0
Stomach, duodenum, small and large	1	0
Small and large	15	0
Colon alone	1 (cecum)	0
Vascular occlusion only	0	3 (all died of hemorrhage)

contribute to the ominous prognosis. Prompt loss of vitality of the thinner colonic wall, less opportunity for collateral circulation, egress of highly infectious large bowel contents into the peritoneal cavity and free perforation present almost insuperable odds (Table III).

A study of etiologic factors highlights the two classes of vascular involvement. Although presented last these features must be kept foremost in view in arriving at a correct and prompt diagnosis. In the arterial group, embolism and thrombosis are considered separately, much as they are in similar situations involving the brain, kidneys, extremities, and heart. Arteriosclerosis is implicated directly or indirectly in about sixteen cases, while rheumatic heart disease with mitral stenosis and thrombus formation in the left atrium or its appendage was the direct cause of embolism in nine cases. Thus the occurrence of an "acute abdomen" with shock in an arteriosclerotic older individual or in a fibrillating rheumatic subject must immediately call to mind the possibility of superior mesenteric artery thrombosis or embolism with massive infarction of the bowel (Table IV).

In contra-distinction to the arterial group the venous variety presents a less clearcut, more variegated, but at times extremely suggestive background. In seven of the twenty cases no etiologic factor could be ascertained, these being the so-called "agnogenic" type so well described by Berry and Bougas (9). In another three, a history, at times remote, of peripheral thrombophlebitis could be obtained. Five cases (four with bowel infarction) occurred in patients who had previously undergone splenectomy. It is well known that thrombocytosis and a tendency for splenic vein thrombosis follow this operation, and spread of the thrombotic process to the superior and inferior mesenteric veins can occur. In the same issue of the *Annals of Surgery* in which Elliot's (3) paper appeared there is a report by Delatour (18) of a case of hemorrhagic infarction of the middle third of the small bowel due to venous thrombosis originating in the splenic vein occurring after splenectomy. Other authors point out the relationship of mesenteric venous thrombosis to splenectomy performed in the recent past or years before. Johnson and Baggenstoss (8) and Whittaker and Pemberton (16) list

TABLE IV

*Mesenteric vascular occlusion: arterial—etiologic factors*

A. Embolic (20)	
1. Rheumatic heart disease; thrombus in left auricular appendage or atrium	9
2. Acute myocardial infarction; mural thrombus left ventricle	2
3. Source of embolus undetermined	5
4. Carcinoma of lung, radiotherapy, thrombus in left atrium	1
5. Mural thrombus left ventricle, cause undetermined	1
6. Paradoxical embolism (peripheral phlebitis, patent foramen ovale)	1
7. Marked sclerosis of thoracic aorta with embolism	1
B. Thrombotic (7)	
1. Thrombosis of superior mesenteric artery	4
2. Severe aortic sclerosis with secondary thrombosis of superior mesenteric artery	2
3. Dissecting aneurysm superior mesenteric artery	1

TABLE V

*Mesenteric vascular occlusion: venous—etiologic factors*

A. With infarction (17)	
1. Undetermined or idiopathic	6
2. Peripheral phlebitis (history)	3
3. Post-splenectomy	4
a. Immediate post-op. period	1
b. Late	
1. 3½ yrs. post-op. splenectomy for acquired hemolytic anemia	1
2. 10 yrs. post-op. splenectomy for Banti's syndrome due to portal vein thrombosis; thrombocytosis due to recent hemorrhage	1
3. 2 yrs. post-op. splenectomy and spleno-renal shunt for cavernomatous transformation of portal vein	1
4. Operative trauma to tail of pancreas and splenic vein in course of left nephro-ureterectomy	1
5. 1 mo. post-op. appendectomy for gangrenous appendicitis	1
6. Polycythemia	1
7. 2½ yrs. post-op. gastrectomy, (?) pancreatitis	1
B. Without infarction (3) (all died of gastro-intestinal hemorrhage)	
1. 2 yrs. post splenectomy for acquired hemolytic anemia; multiple visceral and peripheral thrombi	1
2. Retroperitoneal leiomyosarcoma, sup. mes. v. thr.	1
3. Multiple gall bladder ops. Old recanalized thromboses portal, sup. mes., splenic, inf. mes.	1

this as a possible causative factor. However cause and effect in this situation may be transposed for in two of the cases reported herein the splenectomy was performed for Banti's syndrome in which the primary pathology was portal vein thrombosis and cavernomatous transformation, thus indicating the primary nature of the venous disease. Intra-abdominal infection, a condition frequently referred to by the older authors was found in only one case. The other situations referred to in Table V are self-explanatory.

It is the author's impression that many instances of arterial mesenteric embolism and venous thrombosis may occur sub-clinically without giving rise to

bowel infarction. Occlusion of large arterial intestinal branches has been shown experimentally in dogs by Noer and Derr (7) to be ineffective in causing intestinal infarction. Noer (17) also pointed out the existence of an effective intramural collateral circulation which can compensate for tiny emboli lodging close to the bowel. The one exception to this must be the case of the colon where the intramural circulation is less effective. In one instance in this series an embolus to a cecal artery caused a localized infarct. Cokkinis (19) on the other hand felt that the intramural collateral circulation of the small bowel was quite inadequate to compensate for occlusion of the vasa recta in the adjacent mesentery. On the venous side, the occurrence of areas of thrombosis without infarction is also known to occur. The clinical and pathological picture of "visceral phlebitis migrans" so well presented by Gerber and Mendlowitz (20) attests to this.

#### CASE REPORT

*J. G. Hospital Number 14854.* This forty-seven year old white single Russian-born female was admitted to the Medical Service of the Mount Sinai Hospital for the fourth time on September 14, 1953, with the chief complaint of abdominal pain of nine days' duration and tarry stools on the day of admission.

Her previous admissions were in 1950 and 1951 for hematemesis and melena due to bleeding esophageal varices. At those times diagnoses of hepatic cirrhosis and splenic vein thrombosis were made. Physical findings then included hepatosplenomegaly and, on the first admission, ascites. Blood findings revealed evidence of hypersplenism and liver cell damage. In November 1951 she was operated upon at another hospital where a splenectomy and spleno-renal shunt was carried out. Liver biopsy was allegedly normal and a portal vein block due to thrombosis was found to be present. She did very well following this operation gaining forty pounds in weight.

Nine days prior to this admission she began to experience constant epigastric pain, anorexia, and febrile sensations. After three days the pain became right paraumbilical in location radiating to the back and right shoulder. On the day of admission she passed two tarry stools. Also during these nine days she noted dyspnea on one to two flights, palpitations, and evening ankle edema. There was no jaundice or hematemesis.

Physical examination revealed an obese white female in no acute distress. T 100.2°, P 104, R 19, B.P. 146/80. There was no jaundice. The neck veins were engorged and pulsating. The lungs and heart were essentially normal. The abdomen was not distended. There was tenderness in the epigastrium and the right upper quadrant. Voluntary resistance made palpation difficult. There was no ascites. There was a well-healed left upper quadrant scar of the previous shunt operation.

For the next nineteen days, through October 3, 1953 the patient had a low-grade febrile course uninfluenced by Gantrisin. The highest recorded temperature was 102° but for the most part it ranged between 99° and 101°. During this period she continued to complain of abdominal pain. Among the diagnoses listed on the chart were: Bleeding esophageal varices, subphrenic abscess, perinephric abscess, chronic cholecystitis, bleeding and penetrating duodenal ulcer, pyelonephritis, hyperthyroidism, diverticulitis with perforation, carcinoma of the colon with perforation, and ulcerative colitis. Her ability to undergo X-ray examination of the chest, abdomen, kidneys, and the intestinal tract from above and below attests to the relative mildness of her symptoms. All of these studies were unrevealing.

Between October 3 and October 5 her symptoms worsened markedly. The abdominal pain became more severe, and distention, in part due to ascites, appeared. Her pulse became rapid and finally on the afternoon of October 5 she went into shock. Abdominal puncture in the right lower quadrant yielded bloody fluid which grew out *B. coli*. The leucocyte count rose to as high as 20,600 with 69 per cent segmented forms and 14 per cent bands.

Abdominal films at this time revealed a dilated loop of presumably small bowel in the left upper quadrant, evidence of ascites and some fluid levels.

A diagnosis of mesenteric vein thrombosis with bowel infarction was made by the surgical consultant, and after vigorous blood and fluid replacement therapy the patient was taken to the operating room the evening of October 5, 1953.

*Operation (Drs. Stanley Brodoff and Paul Kirschner):* With the patient under endotracheal cyclopropane anesthesia supplemented by curare a right rectus incision was made. The peritoneal cavity contained a large amount of greenish opalescent and serosanguinous fluid loculated by fibrin. Blackish-red infarcted small bowel presented which when delineated was found to involve only the terminal three and one-half feet of ileum. The limits of this process were poorly and gradually demarcated. The mesentery was extremely edematous, three-quarters of an inch thick, and contained thrombosed veins and vigorously pumping arteries. A resection of the involved bowel with a primary side-to-side anastomosis was effected, and the wound was closed with heavy silk retention sutures after placing drains in the pelvis and right lumbar gutter.

Post operatively she did well. A small transient fecal fistula made its appearance and closed promptly with the aid of sump drainage. The abdominal wound healed well. Heparin and dicoumarol were administered from the fourth through the ninth post-operative days. Intensive antibiotic therapy was administered.

She was discharged in good condition on November 16, 1953. A gastro-intestinal series and barium enema shortly before discharge showed the anastomosis to be about five inches from the ileo-cecal junction.

*Pathology Report #116748 (Dr. A. Bernheim):* Specimen consists of a 105 cm. segment of small bowel. The serosal surface is dull and hyperemic with plastic exudate in some areas. A deep red congested central portion measuring 45 cm. is present. The lumen contains dark red blood mixed with fecal material. The mesenteric veins were filled with clots. Diagnosis: "Segment of small bowel showing hemorrhagic infarction. Lines of resection edematous, acutely inflamed, and hemorrhagic, but not necrotic."

She was last seen in the clinic on September 30, 1954 for unrelated minor complaints and without abdominal symptomatology.

#### COMMENT

This case exemplifies many of the features of the venous type of mesenteric vascular occlusion. There was a previous history of mesenteric vein disease which caused the portal vein thrombosis which in turn occasioned a splenectomy and splenorenal shunt for bleeding esophageal varices. Despite decompression of the portal hypertension by the shunt venous disease struck again this time involving the vessels supplying a long segment of ileum. The splenectomy may have played a role but the pre-existing venous disease contradicts this possible thesis. The characteristic long vague history as seen in many venous cases included a nine day period before admission and a twenty-one day period before the diagnosis was made and surgery carried out. A localized area of involved bowel was present which was amenable to resection and primary anastomosis. Post-operative anticoagulant therapy was employed albeit for a short time. An excellent one year follow-up was recorded.

#### SUMMARY

A series of forty-seven cases of mesenteric vascular occlusion has been reviewed. Twenty-seven of these were due to arterial block, and twenty were caused by venous occlusion. All of the arterial and seventeen of the twenty venous cases



resulted in infarction of the bowel. The common result of either arterial or venous mesenteric occlusion is hemorrhagic infarction of the intestine.

The arterial group usually resulted from either embolic or thrombotic occlusion of the superior mesenteric artery, the major etiologic factors being rheumatic heart disease with mitral stenosis and auricular fibrillation, or being manifestations of arteriosclerosis. The extent of bowel infarction was massive, the clinical picture explosive in its evolution, and, in this series, the outcome uniformly fatal.

The venous group usually involved shorter segments of bowel (small intestine), was slower in development, was more difficult to diagnose, but despite this yielded six recoveries out of ten operations. These were the only survivals in the entire group of forty-seven patients. Most of the venous cases fell into the "agnogenic" group in which no etiologic factor could be ascertained, while the next most common type bore some relationship to a previously performed splenectomy—recent or old. Three of the venous cases were unassociated with bowel infarction, but all died of massive gastro-intestinal hemorrhage.

A case of mesenteric venous thrombosis with hemorrhagic infarction of the ileum is presented to exemplify the less well-known venous type. Recovery followed resection of the infarcted bowel.

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## CHRONIC TUBO-OVARIAN COLONIC FISTULA

### REPORT OF AN UNUSUAL COMPLICATION OF TUBO-OVARIAN ABSCESS, AND ITS OPERATIVE MANAGEMENT

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A persistent communication between a pyosalpinx or tubo-ovarian abscess and the sigmoid colon is a rarity. Only one such case secondary to pelvic inflammatory disease has been reported in the recent literature (1).

Croce (1) in 1947 reviewed the literature and failed to find a report of any case with an intestinal fistula above the rectum or recto-sigmoid. He then presented a case of acute bilateral pyosalpinx which spontaneously established a chronic fistulous communication between the left Fallopian tube and the sigmoid colon. A preoperative barium enema roentgenogram included in the report demonstrated the fistulous tract with entry of dye into the left pyosalpinx. Surgery was deferred for six months until the acute stage of the disease was passed, and at that time a fistula was found between the distal end of the tube and the sigmoid. According to plan no further pelvic procedure was performed, but a double barreled spur type colostomy was established. The isolated distal segment was irrigated daily and forty-eight days later proctoscopic examination revealed marked improvement in the previously inflamed segment, and the internal orifice of the fistula was clearly visualized. Seventy days post operation the fistula was found to admit the tip of a finger and the fistulous orifice in the sigmoid was closed with two purse-string sutures. The left tubo-ovarian mass was then ablated. Six months after the primary operation the colostomy spur was reduced by a spur-crushing clamp followed a month later by an extraperitoneal closure of the colostomy. Pathological examination revealed non-specific inflammatory disease of the tube.

We have no knowledge of any other report of a tract between a tube or tubo-ovarian abscess and the sigmoid colon except one reported by Vesell (2) in 1948. He discovered a salpingo-sigmoidal fistula by means of a routine hysterosalpingogram done in evaluating a sterility problem in June 1945. However, in this case there was no antecedent history or physical findings suggesting pelvic inflammatory disease. Included in his presentation are X-rays clearly demonstrating the passage of lipiodol from the tube to the rectum, via the sigmoid. Three months later a barium enema and chest plate were negative, and seven months later a repeat hysterosalpingogram revealed non-patency of both tubes.

Up until the present time the patient has not conceived and no apparent etiology has been discovered to explain the unusual fistula.

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## CASE REPORT

A 28 year old grava 0, para 0, single Negress was admitted to The Mount Sinai Hospital, October 30, 1950, complaining chiefly of pain in the right lower quadrant of 6 months' duration. At that time, she was told that she had an inflammation of her tubes. For a few months before admission, the patient noticed rather severe, dull, aching, right quadrant pain unassociated with meals and most prominent and severe at the time of her menses. The pain usually began about four days before her period with great relief at the onset of flow. Her periods were normal in amount and duration. Aside from slight, occasional constipation, there were no abnormalities in her bowel habits. There was no history of melena, tenesmus, vomiting, nausea, dark stools, or hematemesis. Six months prior to admission, the patient had been treated with penicillin for a luetic infection.

On admission, the patient complained of pain in the right lower quadrant. She also noted a very slight vaginal spotting for one month. There was no post-coital spotting and no hormones were taken at any time. Laboratory studies: hemoglobin 11 grams, white blood count 8,000, normal differential. ESR 10 mm per hr, urine: negative, Pap. smear negative, Wassermann negative, blood urea nitrogen 10, fasting blood sugar 75. On physical examination, the head, lungs and chest were normal. There was a soft tender mass in the right lower quadrant. Pelvic examination revealed a small sinistverted uterus, behind which and to the right, there was a tender cystic mass the size of a small orange.

*Course:* Laparotomy was performed under general anesthesia. The uterus was bound down by adhesions, retroverted and small. The left adnexa showed clubbing of the tube, but was relatively free. The right tube was found to be thickened, its fimbriated end enclosed in a mass the size of an orange, on the surface of which ovarian tissue could be seen. The mass was fluctuant, situated in the right cul-de-sac, lying over and closely adherent to the recto-sigmoid. It was moderately free laterally. The broad ligament on this side was clamped close to the uterus, and the infundibulo pelvic ligament was clamped, cut and ligated. The adnexae were then freed except the adherent portion joining the recto-sigmoid. This was attached by a small, finger-like projection, approximately 1 cm. in length. On attempting to remove this by sharp dissection, a small amount of foul-smelling pus exuded into the field which on culture revealed *B. coli*. The mass was then removed by sharp dissection. Examination with a probe revealed the bowel to be continuous with the small, finger-like diverticulum. The defect was closed with two purse-string sutures of 00 chromic catgut. This was reinforced by three layers of sutures through the muscularis and serosa. The left tube was then resected and the round ligaments were brought over the cornual angles for reperitonization, suspending the uterus anteriorly. A cigarette drain was placed at the site of closure and taken out through a right lower quadrant stab wound. The patient received procaine penicillin and streptomycin postoperatively and had an uneventful recovery, the temperature never rising above 100 degrees. The clips were removed on the fifth postoperative day. The drain was shortened on the seventh day, and removed on the eighth postoperative day.

The pathology report revealed tubal segments with chronic salpingitis. The right ovary revealed a cystic structure with a fibrous wall and granulation tissue lining. The patient was discharged on the thirteenth postoperative day, completely asymptomatic.

A barium enema examination with the aid of air insufflation 12 weeks postoperatively failed to disclose any evidence of an intrinsic organic lesion in the large bowel. Pelvic examination 14 months postoperatively was normal.

## COMMENT

A pelvic abscess secondary to acute salpingitis most frequently points in the posterior cul-de-sac of Douglas. Spontaneous rupture of such an abscess may occur in the rectum at this point. When the opening is direct and large enough



and lies at the bottom of the sac spontaneous closure is most common. If the abscess opens into the bowel by a long sinus or if the opening is in the upper part of the abscess, so that the pus only discharges when the sac is full, the discharge may go on indefinitely. If such an abscess of the pelvis is drained through the posterior fornix of the vagina, a recto-vaginal fistula or a recto-peritoneo-vaginal fistula may result. Fistulous communications, secondary to pelvic inflammatory disease have been reported in association with the rectum, vagina, bladder, (3) abdominal wall, uterus (4) and retroperitoneal spaces, and rupture of a pelvic abscess may also occur into any of these organs. When the bladder is perforated a large amount of pus may escape through the urethra. Abscesses may open into the vagina, completely empty themselves and heal spontaneously; however, when a fistulous tract is tiny, the discharge of purulent material can only take place when the pressure is sufficient to overcome the resistance and in this way may continue for months or years.

Wharton (5), in 1921, in his paper on pelvic abscesses, reported a series of 716 cases over a period of 23 years. Of these, 462 cases were treated by vaginal incision drainage only and 170 cases by both vaginal and abdominal operation. It is of interest that there were no instances of rupture into the sigmoid, but in two cases intestinal obstruction was caused by the pressure of the abscess on the rectum and sigmoid.

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## SPONTANEOUS HYPOGLYCEMIA

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Spontaneous hypoglycemia denotes an abnormal lowering of the blood sugar level, frequently attended by a distinct group of symptoms, and not produced by the administration of exogenous drugs, chiefly insulin. Harris (1) in 1924 was the first to describe such a syndrome, calling it hyperinsulinism, and noted its similarity to that of hypoglycemic shock induced by an overdose of insulin in diabetic patients. It was not until 1927 that Wilder (2) was able to show a cause and effect relationship between hyperinsulinism and the hypoglycemic syndrome by demonstrating a high insulin content in a metastatic nodule in the liver of an islet cell carcinoma of the pancreas, the alcoholic extract of which depressed the blood sugar when injected into rabbits. Now the literature contains many reports of surgical cures following resection of islet cell adenomas. Joslin (3) in 1928 first described the underlying physiological mechanism of this syndrome. He postulated that "by lowering the blood sugar certain oxidative processes become depressed to such a degree that the brain cells are affected in much the same manner as in asphyxia."

However, there exist many disease entities in which hypoglycemia with its concomitant symptoms may occur. This group may be subdivided into two etiological headings, organic and idiopathic or functional. The term functional hypoglycemia is a poor one as pathological change undoubtedly exists but we are unable to demonstrate it by present day anatomical methods. Conn's classification (4, 4a) with minor modifications, is probably the most inclusive one and is reproduced here in abbreviated form:

### I. Organic hypoglycemia

#### 1. Endocrine causes

##### A. Pancreas (hyperinsulinism)

a. Islet cell adenoma or adenocarcinoma, adenomatosis

b. Islet cell hypertrophy or hyperplasia

##### B. Hypopituitarism (anterior lobe)

##### C. Adrenal cortical insufficiency

##### D. Hypothyroidism

#### 2. Hepatic diseases

##### A. glycogen diseases

##### B. fatty metamorphosis

##### C. diffuse intrahepatic cholangiolitis

##### D. toxic hepatitis

#### 3. Central Nervous System Diseases

##### A. hypothalamic lesions

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## B. brain stem lesion

## II. Idiopathic hypoglycemia

1. Autonomic nervous system imbalance (? increased vagal tone)
2. Alimentary tract disturbance (diminished absorption due to enzymatic dysfunction or hyperperistalsis with shortened passage time)
3. Renal glycosuria
4. Post operative hypoglycemia
5. Lactation
6. Exhaustive muscular exertion
7. Starvation

About eighty to ninety per cent of all cases of spontaneous hypoglycemia are due to islet cell tumors, liver disease and idiopathic causes. Since the less common causes and liver disease are fairly easily ruled out, the differential diagnosis usually rests between idiopathic hypoglycemia and islet cell adenomas of the pancreas. Few patients with cirrhosis of the liver or hepatitis develop hypoglycemia whereas fatty metamorphosis of the liver is said to be a much more frequent cause and a low blood sugar is invariably found in patients with von Gierke's disease.

Despite the rapid recognition of hypoglycemia as a clinical entity following Harris' paper, rigid diagnostic criteria were not laid down until the late 1930s, when Whipple (5, 5a) postulated his classical triad of criteria which should really be expanded into a tetrad, namely (a) gastrointestinal and central nervous system symptoms with (b) a fasting blood sugar of fifty mg. per cent or less or abnormally low post absorptive blood sugar levels, (c) immediate and dramatic relief of symptoms by the administration of sugar. The last point may not necessarily hold if hypoglycemic coma is prolonged, and (d) a characteristically abnormal electroencephalogram which reverts to normal within a matter of minutes after the administration of intravenous glucose.

## DIFFERENTIAL DIAGNOSIS

By idiopathic hypoglycemia we mean an excessive functional sensitivity and responsiveness of histologically normal islet cells to the normal stimulus for insulin secretion. Proof for this lies in the fact that increasing the carbohydrate intake of normal animals results in increased blood insulin levels and vice versa (4). This has also been demonstrated by injecting glucose into the arteries of the pancreas in experimental animals and then finding a definitely elevated insulin content of pancreatic venous blood (4). Patients in this category usually do not give a progressive history. Their symptoms are easily exacerbated by emotionally charged situations and although they frequently have normal fasting blood sugars their attacks occur two to four hours postprandially and are not aggravated by fasting. The glucose tolerance curve shows a normal rise with a rapid fall within two to four hours to sub-normal levels, but usually there is a spontaneous rise after four to five hours (4, 6). Such patients respond well to a diet high in protein and fat and low in carbohydrate (77). A high carbohydrate content in the diet is mandatory in hepatogenic hypoglycemia, as here the basic defect is one of

impaired glycogen storage or glycogenolysis. In liver disease the lowest blood sugar is found after the longest period of fasting, i.e. just before breakfast, which is sometimes referred to as early morning confusion. The glucose tolerance curve in these patients starts off with a very low value but subsequently rises to a high plateau presumably because the decreased rate of glycogenolysis keeps the blood levels of absorbed sugar at higher levels for a longer period of time than is normally found in the initial post-prandial stage. The high plateau is followed by a gradual fall to subnormal levels four to seven hours post-prandially, without a spontaneous return to normal values. Generally speaking these patients are also intolerant to long fasts or carbohydrate restriction and usually manifest no significant rise in blood sugar in response to epinephrine (4, 4a, 6, 7). Occasionally after gastrectomy or gastroenterostomy the patient has a normal fasting blood sugar which rises to hyperglycemic levels one hour post-prandially only to fall precipitously during the second and third hours (8). Evenson has been able to demonstrate a similar curve in a group of normal controls by feeding dextrose via a duodenal tube. He postulates that alimentary functional hypoglycemia really represents a normal response of a normal pancreas to an abnormally great stimulus; and he therefore advocates the prevention of post-prandial hypoglycemia as one of the cardinal features of therapy in this disorder (9).

Crain and Thorn (10), reviewing 258 cases of functioning islet cell adenomas of the pancreas, found the age incidence to range between six and a half weeks and sixty-eight years. The history was frequently progressive and twenty-five per cent of patients had symptoms for over five years. Should the history be brief and progressive, an adenocarcinoma of the islets of Langerhans must be considered. Almost any type of glucose tolerance curve has been described in patients with organic hyperinsulinism, diabetic ones not being infrequent (4, 6, 10). These bizarre variations have led many clinicians and investigators not to depend on this test (7, 8, 10). However, Conn insists that such a test can be of diagnostic value if properly standardized. He advocates a liberal caloric diet, including the ingestion of 250 Gm. of carbohydrate, daily for three days preceding the tests. Under such conditions he found the post-absorptive blood sugar levels in cases of true hyperinsulinism to be uniformly fifty mgs. per cent or less, a peak rarely exceeding 120 mgs. per cent and a fall to subnormal levels by the end of the second post-prandial hour and remaining there up to six hours. The Ann Arbor group never found such a curve in hepatogenic or idiopathic hypoglycemia (6). Insulin sensitivity and tolerance tests have proven unreliable in the hands of many investigators (10-13). It is plainly evident that no single reliable criterion exists. Repeated fasting blood sugars should be drawn. A blood sugar at the onset of an hypoglycemic attack may be most informative, for if there is a convulsion the blood sugar at the end of the attack may be normal or even elevated. The glucose tolerance test is of significance mainly if the fasting level is normal or if no sample can be obtained at the beginning of the seizure. If clinically suspected hypoglycemia cannot be demonstrated by the methods indicated an eighteen to twenty hour fast with blood sampling every four hours should be undertaken. In organic hyperinsulinism it is the rapidity of the fall in blood sugar levels that produces



the symptoms, not the level itself (4, 11). This may help to explain why more spells occur in the daytime and in relation to meals than at night when the actual blood sugar is the lowest, but this low point is obtained relatively slowly.

#### CLINICAL SYMPTOMS

Almost every clinical neurological symptom, diffuse or focal, has been described in hypoglycemia. A distinguishing feature of a hypoglycemic seizure is its slow, gradual onset. Temporary confusion, headaches of any nature, light-headedness, lethargy, profuse perspiration, generalized tremor or bizarre automatic movements which may finally run into frank convulsions are commonly seen. Transient paresis, peripheral neuritis, pathological reflexes and aphasia are also frequent findings (8, 10, 15, 16, 17, 79). Depending on the severity of the picture, loss of consciousness, coma and death may occur. Gastrointestinal symptoms, mainly hunger, may or may not be present. If so they usually do not follow a definite pattern. Symptomatic angina pectoris with T wave inversion on the electrocardiogram and cardiac arrhythmias have been reported in isolated instances (18, 19).

The lumbar puncture is not revealing and yields normal or even elevated spinal fluid sugar levels. Since hypoglycemic reactions develop in various patients at different blood sugar levels, the presence of a borderline sugar value can neither prove nor disprove a causal relationship between alterations in blood sugar and the appearance of neuropsychiatric symptoms in a given case (20, 22, 23, 23a). In such instances as well as in more manifest ones it has been shown that the electroencephalogram may reveal such a correlation (21). Classically the following changes appear as blood sugar levels decrease progressively: (a) Delta activity appears during hyperventilation in subjects which did not show such activity when hyperventilated at high blood sugar levels. The lower the blood sugar level the greater is the effect of hyperventilation on the tracing. (b) Alpha activity gradually diminishes in frequency. (c) Symmetric, diffuse bursts of delta activity, frequently of high voltage, appear. (d) More or less continuous diffuse and more or less symmetrical slow activity prevails with or without superimposed delta activity (20). The lowering of the alpha frequency owing to a depressed blood sugar can, to some extent, be counteracted by oxygen administration. Strauss and Wechsler (21), in a study of hypoglycemic patients, have shown that in fast-ing electroencephalograms without delta activity, such delta waves appear after two minutes of hyperventilation and that this can be abolished by intravenous sugar administration. Their studies on 111 patients revealed that high blood sugar values tend to prevent the development of slow activity on hyperventilation and that the hyperventilation induction time varies directly with the blood sugar level. While electroencephalograms of people under thirty-five years of age are more apt to show delta activity with decreased blood sugar levels, here as well as in other groups many individual differences exist (20). Even extremely low blood glucose levels cannot produce an epileptic type of brain activity but may produce additional changes in previously abnormal electroencephalograms.

Several authors (24, 25) describe the precipitation of three per second spike and dome pattern in known epileptics.

In addition to the bodily symptoms, characteristic psychologic concomitants such as dullness of consciousness, weakness in concentration, abulia, acts of immorality and a depressed or anxious state of mind may be present. Anxiety may or may not be present depending on a person's personality makeup (26). Repeated severe attacks may result in persistent and progressive mental deterioration. Szondi and Lax (27) studied thirty-one neurotic patients, who were classified as "neurasthenics". These patients received fifty gms. of glucose by mouth and it was shown that the glucose tolerance curves were relatively flat as compared with those of a group of control subjects. This led to the assumption that in psychoneurotic patients the regulatory mechanism of alimentary glycemia is impaired. Portis (28) suggests that the neurasthenic symptom complex per se may be responsible for the low blood sugar rather than vice versa.

#### FACTORS INFLUENCING THE BLOOD SUGAR LEVEL

Multiple factors exert their influence on carbohydrate metabolism. Regulation of blood sugar levels is mainly dependent on an intact liver and on a balance of endocrine secretions. ACTH, cortisone and hydrocortisone increase the deposition of glycogen in the liver by enhancing gluconeogenesis from amino acids and by interfering with the peripheral utilization of sugar by depressing the hexokinase reaction. The diabetogenic quality of the growth hormone of the anterior pituitary is well known and recent observations suggest that it, like other insulin antagonists, interferes with the binding of insulin by muscle (29-31). After the withdrawal of ACTH and cortisone, following the prolonged use of these compounds, patients may experience periods of relative hypoglycemia due to persistence of the excessive insulin secretion formerly necessary to utilize the raised blood sugar. Suddenly increased demands for glucose are probably met by the liberation of additional adrenalin which temporarily augments liver glycogenolysis and may also aid in the breakdown of muscle glycogen and in the formation of lactate. While the hypoglycemia in myxedema is probably due to poor absorption of foodstuffs from the gut, it has been shown that hyperthyroidism is associated with increased glucose absorption from the intestine and thus may even aggravate previously existing diabetes (32-34). The major effect of insulin is probably its acceleration of the breakdown of glucose to lactate and pyruvate as well as a speed-up of the complete oxidation of glucose to carbon dioxide and water, which it does by promoting the hexokinase reaction and thereby neutralizing the inhibitory effects of ACTH and cortisone (31). Furthermore, it promotes gluconeogenesis and also lipogenesis from glucose and acetate in the liver and in other tissues, prevents the accumulation of fat in the liver (unlike the fatty changes so frequently found in diabetic livers), maintains depot fat and suppresses the formation of ketone bodies (35). Lately it has also been demonstrated that insulin may influence the rate of entry of some sugars into the intracellular compartment (31). Glucagon, a hyperglycemic factor, has recently

been extracted from the alpha cells of the pancreas. Its physiological action appears to be quite similar to that of epinephrine in that it acts on hepatic phosphorylase and thus favors glycogenolysis (31, 36). The relative mildness of diabetes following total pancreatectomy may possibly be due to the removal of this hyperglycemic factor.

Neurogenic factors also influence the blood sugar level, although most investigators seem to agree that the blood sugar level is the crucial factor in determining the amount of insulin secreted. LaBarre (37) and associates are the foremost proponents of the vagal stimulation theory. After showing that the normal blood sugar level of a dog may be reduced by transfusing the blood from a pancreatic vein of another dog during stimulation of its right vagus nerve, they postulated an insulin regulatory center in the thalamus which was affected by glucose concentrations in the blood and transmitted its impulses via the vagus to the beta cells of the pancreas. The group went on to claim that if the thalamus of such hyperglycemic animals was destroyed or removed the hyperinsulinism also disappeared (38). This work has never been confirmed or duplicated.

#### CEREBRAL METABOLISM

Since the majority of hypoglycemic symptoms are neurological in nature a brief review of cerebral metabolism seems indicated. The brain needs energy for trophic as well as for conduction purposes. While the brain of the fetus and lower primates derives a small percentage of its energy from anaerobic carbohydrate metabolism, the adult brain is almost wholly dependent on the oxidation of glucose. Certain non-carbohydrate substances such as lactate and pyruvate, which may be converted to glucose in the liver, cannot be utilized by the brain of hepatectomized animals (39). In vivo the cerebral respiratory quotient is 1.0 indicating that carbohydrates are oxidized exclusively (40). Furthermore, in man the oxygen consumption of the brain can be accounted for entirely by the oxidation of glucose absorbed from the blood passing through the brain (14a). Unlike all other organs in the body the brain does not require insulin for its oxidation of sugar (40).

The energy demands of the brain during hypoglycemia are met by: (a) the formation of glucose from cerebral glycogen, (b) a change in the peripheral utilization from glucose to fat by non-nervous tissue, (c) hepatic glycogenolysis. Actually, the last mechanism is the most important and if the liver is sufficiently damaged the other two factors cannot maintain the requirements of the brain (14b).

Himwich and Frostig (14c, 41, 42) divide the symptoms of acute hypoglycemia into five phases and correlate their sequence with the depression of the metabolic rate at various levels of the brain. These stages of the hypoglycemic response were observed during insulin shock therapy on schizophrenics and occur in this order: (A) Cortical phase: it is characterized by inattention, clouded consciousness, sweating, salivation and tremors. It may or may not show mild excitement. (B) Subcortical-diencephalic phase: it occurs once integration at the cortical level has broken down. It is the phase of maximal sympathetic activity and is

characterized by motor restlessness and automatic movements. As the patient lapses into unconsciousness the alpha waves of the electroencephalogram disappear completely and are followed by slower undulations which continue during the remaining stages of hypoglycemia without necessarily being an indicator of any particular phase (22, 41). (C) Mesencephalic phase: The characteristic findings of this stage are tonic and torsion spasms and the occurrence of pathological reflexes, i.e. Babinski phenomenon. The pupils are frequently dilated and usually do not react to light. The eyes may move disconjugately at the end of this phase. (D) Premyelencephalic phase: here one finds tonic episodes, chiefly extensor in nature, simulating a decerebrate posture. (E) Myelencephalic phase: this is one of deep coma, extreme hypotonia, depressed deep tendon reflexes and absence of the corneal reflexes. This chronology and the reverse order in which the various phyletic layers are brought back into function indicate that the cortex is the most and the medulla and spinal cord the least sensitive layers (42).

Lacking glucose, brain metabolism is decreased as evidenced by a decreased arterio-venous oxygen difference while the cerebral blood flow remains constant or even rises (43, 44).

Although cerebral blood flow seems to be adaptive, it is not so to the extent of keeping arterio-venous oxygen differences constant. Thus it is probably cerebral anoxia which is the immediate factor in the production of hypoglycemic symptoms (43, 45). Feldberg (46) has shown that hypoglycemic blood levels may enhance the rate of acetylcholine production the release of which might act as another cerebral irritant. However, the experimental evidence here is incomplete. It is not feasible to measure the utilization of sugar by the brain by determining the rate of supply of glucose but rather by determining the magnitude of cerebral consumption of this foodstuff in relation to its energy needs. Thus the lack of clinical symptoms even when the blood sugar is critically depressed, as may occur in infants, can be explained either, by (a) a low blood sugar does not necessarily mean a similarly low brain sugar or (b) a low blood sugar does not critically affect a brain with relatively low energy requirements. The last point seems to be confirmed by drowning studies wherein a good percentage of young children who had been apneic for six to fourteen minutes recovered completely while adults never recover from such prolonged asphyxia (47-49). Experimental work in animals whose blood sugar was lowered under anesthesia produced no clinical symptoms, yet the same experiment without anesthesia did yield convulsions (50). Clinical and laboratory studies of insulin hypoglycemia have shown that the brain has the ability to absorb as well as to release sugar. It was found that the oxygen saturation of venous blood was equal to and even higher than that of arterial blood (in the absence of AV shunts) and that the sugar content of venous blood frequently exceeded that of its arterial counterpart (11). The failure of blood glucose to enter the brain may be one cause for the production of prolonged shock and may be due to deprivation of energy and to a breakdown of such energy-requiring processes as phosphorylation of sugar which is necessary for the passage of the molecule across the cell membrane. Yet, while the normal brain cell is relatively impervious to the entrance of electrically charged ions,



in hypoglycemic coma the permeability of the nerve cell to electrolytes, but not to glucose, is enhanced. Sodium enters the cell and produces a shift of water, which explains the edema so often found at necropsy. Potassium, on the other hand, seems to migrate out of the cell, thereby further retarding its oxidative processes (51).

The frequent occurrence of reactions at comparatively high sugar levels raises the question of a reaction threshold (52). In a study of 1000 cases of diabetics with insulin reaction, the blood sugar was found to be normal or high in fifty per cent. It is also well known that patients who had been starved or had a concomitant serum calcium deficiency have unusually high insulin sensitivity (53).

Under normal conditions the sugar content of the blood is higher than that of the cerebrospinal fluid, the ratio being roughly two to one (11). In insulin hypoglycemia the sugar concentration in the cerebrospinal fluid remains unchanged or may even be increased (54).

Reports of successful treatment of hypoglycemia with vasodilators suggest that vasoconstriction may occur. Yet no one has been able to show significant changes in cerebrovascular resistance during hypoglycemia (43-45). The decreased cerebral oxygen consumption despite a fair constancy in blood flow indicates that here, as in narcosis, the normal intrinsic adjustment to metabolic requirements is upset. But since cerebral vessels are terminal structures one cannot postulate a narcotic weakening of smooth muscle in the vessel wall. We are probably dealing with a shift in the metabolic pathways of the brain leading to the presence of abnormal metabolic products. This is supported by the fact that cerebral glucose consumption in one case of coma fell eighty-three per cent while the oxygen uptake fell only forty-five per cent (44); and since the brain uses glucose almost exclusively, it must be consuming its own carbohydrate stores. Despite the discrepancy of diminished arteriovenous oxygen difference in the face of a stepped up blood flow, there is good correlation between the degree of cerebral dysfunction and the extent of diminution in cerebral oxygen consumption (14d). The latter is reduced an average of nineteen per cent in subjects who showed varying degrees of mental confusion but did not lose consciousness, whereas patients in hypoglycemic coma had a forty per cent reduction in oxygen consumption. The oxygen requirement of the normal adult brain is about forty-six to fifty-three cc per minute, which represents approximately eighteen to twenty-one per cent of the body's total oxygen consumption at rest. A minimum of twenty-five per cent of the normal cerebral metabolic rate is necessary to maintain the structure of the brain and operation of vital centers in the medulla (14d).

Irreversible reactions resulting from severe and prolonged hypoglycemia include edema, punctate hemorrhages, and necrosis of the cortex characterized by degeneration and disintegration of ganglion cells, as well as swelling of the glia and axis cylinders (55-59). Experiments in cats have shown that ten second anoxia produces no pathological change; three minute anoxia causes frank necrosis in small and limited areas; seven and a half minutes of complete anoxia may destroy the cortex almost completely, with laminae III and IV most sus-

ceptible, followed by the Purkinje fibers of the cerebellum, while the brain stem and cord are last involved (60). Experimental severe hypoglycemia in monkeys of three and a half to four hours duration produces acute swelling and vacuolation of nerve cells; after nine and a half hours the changes become permanent, and after fourteen and a half hours the entire cytoplasm of the cell disappears and only nuclei remain and an increase in the number of glial fibers is noted (61).

#### PATHOLOGY

Not all islet cell adenomas of the pancreas produce clinical symptoms. Duff found that more than fifty percent of his series of such adenomas represented chance findings at autopsy and that only sixty-four of ninety made themselves clinically manifest (62). The incidence among the sexes is about equal. Crain and Thorn reviewing 258 cases of functioning islet cell adenomas of the pancreas found that twelve percent of the patients had multiple adenomas most of which were located in the body or tail (10). Yet this does not exonerate the head of the pancreas, which is difficult to expose, and adenomas missed at surgery have subsequently been found deeply imbedded in the head of the pancreas at autopsy (10). Reports on the size of various adenomas range from two mm. to fifteen cm. (10, 63). It must be stressed that the size of the tumor bears no direct relationship to the severity of the clinical picture. Of 258 cases, 190 were benign, 44 showed questionable histological evidence of early malignancy, while 24 had definite metastases. The latter, although disseminated, seemed to show some predilection for lymph nodes and liver. Frantz has reviewed the histology of these tumors and points out that the differentiation between benign and malignant islet cell tumors is often difficult (64). Islet cell adenomatosis may exist alone or in conjunction with adenomatous changes in other endocrine glands (65, 80, 81). Here many small diffusely scattered nodules are found in the pancreas. Histological examination shows hyperplasia, hypertrophy or a ribbon-like arrangement of cells. Such findings have been reported in the pancreas of a child born to a diabetic mother and may possibly represent a reaction to the increased maternal demands during pregnancy (66).

#### CASE PRESENTATIONS

*Case 1.* H. V., a 78 year old white housewife, entered the Mount Sinai Hospital for the first time on July 27, 1954 because of episodic loss of consciousness of four months duration. She had been in excellent health all her life, never consulting a physician until her present illness. Four months prior to admission she sustained an unexplained fall with minor injuries to the right shoulder. Six weeks later she fell again, this time bruising her hand. The patient attributed both falls to "stumbling in the dark" despite the fact that both accidents had occurred in mid-morning and mid-afternoon respectively. No history of head trauma, headaches, vertigo, visual difficulties or staggering gait could be elicited. About one month before her admission the patient was found unconscious on the floor of her apartment and was seen almost immediately by her physician who noted complete aphasia, right hemiparesis and a right Babinski. These signs cleared spontaneously within four hours. Except for amnesia for this and all subsequent episodes, the patient was perfectly lucid and normal during the interval periods. During the next three weeks the patient suffered four more episodes of syncope lasting anywhere from a few minutes to three hours.

They occurred at no particular time of day and were not related to hunger. There was no preceding aura. The attacks themselves were characterized by profuse perspiration, a generalized tremulousness, but no true convulsive movements or tongue biting. Urinary incontinence was present on at least one occasion. Following the seizures the patient appeared slightly lethargic for a few minutes. The family described the patient as a stable and not particularly emotional individual. The family history disclosed one twenty-eight year old grandchild to have had an episode of syncope at age twenty-one which was said to have been caused by a "low blood sugar and cured by sugar and a diet" without further recurrences. Blood sugar determinations done on the patient's six children and four of her grandchildren fell in the sixty-five to ninety milligrams percent range.

*Physical Examination:* Temperature 99°F, BP 134/88, pulse 118, regular. Late expiratory wheezes were heard over the entire left chest. The heart was enlarged to the left anterior axillary line in the fifth left intercostal space, but the heart sounds were good and regular. No murmur, rub or gallop was heard. A<sub>2</sub> was louder than P<sub>2</sub>. The liver edge was felt three finger breadths below the right costal margin and was not tender. All peripheral pulses were patent. A mild cystocele was noted. The neurological examination was entirely normal except for equally sluggish deep tendon reflexes in both lower extremities, diminished perception of vibration below the right knee and over the dorsum of the left foot.

*Laboratory:* Hemogram and urinalysis were within normal limits. The sedimentation rate was fifty-six millimeters after one hour. Blood and spinal fluid serology were negative. Blood urea nitrogen, sodium, potassium, carbon dioxide, chloride, calcium, phosphorus as well as a complete battery of liver tests were within normal limits. Repeated fasting blood sugar determinations revealed values of 40, 47, 51, 37, and 33 milligrams percent. Oral glucose tolerance test at zero, 30, 60, 120, 180 and 240 minutes revealed values of 40, 156, 212, 122, 77, and 33 milligrams percent respectively. This curve, except for the one hour peak, was essentially duplicated by an intravenous glucose tolerance test. There was no spillage of sugar in the urine. Insulin sensitivity and tolerance studies showed no abnormal trend. Iodine-131 uptake was normal. The electrocardiogram revealed left axis deviation, an atypical right bundle block and evidence of an old diaphragmatic infarct. Serial tracings taken over a four week period showed no changes. There was no undue carotid sinus sensitivity. A two meter chest film showed the heart to have an enlarged transverse diameter and also revealed the presence of a round, sharply delineated shadow in the posterior mediastinum, presumably a neurofibroma. Bronchoscopy was negative. Skull films showed generalized hyperostosis. The sella was normal in appearance and size. X-ray studies of the upper and lower gastrointestinal tract were within normal limits. Lumbar puncture revealed normal manometrics, absence of cells and a spinal fluid sugar of 54 mg. Spinal fluid protein and chloride determinations were normal.

*Course:* While in the hospital the patient never experienced any episodes of syncope. During the course of a gastrointestinal x-ray examination, at a time when the patient had gone without food for about fifteen hours, she became quite agitated, tremulous, perspired profusely and complained of hunger and a severe generalized headache. Blood sugar drawn at that time was forty-five milligrams percent and the symptoms were almost immediately abolished by the ingestion of 240 cc. of sweetened orange juice. An admission electroencephalogram taken immediately after breakfast was read as normal. However a similar tracing following a twelve hours fast revealed many brief, high voltage bursts of two to four/second activity diffusely, but more frequently over the left temporal area. Hyperventilation greatly increased the number of diffuse bisynchronous bursts of slow activity. Within five minutes after the injection of ten grams of glucose intravenously, the record became completely normal and hyperventilation was without effect. No more food was given to the patient and after two hours rare bursts of slow activity appeared which became more frequent as time progressed. One hundred and sixty minutes following the injection of glucose the record was similar to the fasting electroencephalogram and a blood sugar drawn at that time was thirty-three milligrams percent.

*Discussion:* In view of the patient's age, the recent onset, the non-progressive history, the absence of demonstrable hepatic, gastrointestinal, endocrine or central nervous system dysfunction, and the lack of correlation of these episodes of syncope with hunger states, it was felt that a pancreatic islet cell adenoma was unlikely and that this patient represented a case of idiopathic or functional hypoglycemia. She was given a 1500 calories, high protein and fat and moderately low carbohydrate diet on which she has been asymptomatic for the past three and a half months except for a brief period of confusion readily relieved by the ingestion of orange juice.

*Case 2.* G. G., a 71 year old white housewife, was admitted to the Mount Sinai Hospital on October 8, 1953 because of recurrent attacks of unconsciousness during the previous five months. The patient, a para four, grava four, had been admitted on several occasions because of recurrent renal calculi, pyelonephritis and persistent menorrhagia for which she had received radium treatment in 1937. Mild hypertension had first been discovered five years prior to the present admission. Her current illness consisted of recurrent attacks of apparent loss of consciousness, bizarre coordinate movements of the arms, waving her hands in the air and frequent wiping of her brow. There was never any loss of sphincter control. Other times the patient would just stare straight ahead, hold her head with her hands and would not respond to questions. These episodes lasted anywhere from thirty minutes to two or three hours, but the patient was always perfectly lucid during the interval periods. The history suggested no obvious relation to lack of food intake or meal times, but the episodes would occur in daytime only. The family history disclosed that a brother and a son of the patient had asymptomatic pentosuria.

*Physical Examination:* At the time of admission the patient was semi-stuporous but would respond to her name by looking up for a few seconds. She remained in this state for sixty hours during which time she took in very little food. She was afebrile, her pulse was 84 and regular and her blood pressure varied between 150/90 and 210/100. Except for the heart being slightly enlarged to the left, the examination was not remarkable. Neurological evaluation revealed both pupils to be round, equal and to react to light. All deep tendon reflexes were intact and no pathological reflexes could be elicited. There was no obvious motor weakness and all limbs withdrew equally from noxious stimuli. On the third hospital day the patient was alert and oriented but could not recall her seizure. At this time bilateral Babinskis and Chaddock's were found and one observer felt that there was increased tone in both right extremities.

*Laboratory:* Hemoglobin 11.4 grams, WBC 7500, with a normal differential count. Sedimentation rate was fifty-three millimeters after one hours. Urinalysis was normal except for one plus albuminuria. The blood urea nitrogen was twenty-nine milligrams percent but serum electrolytes, calcium, phosphorus and a complete battery of liver chemistries were within normal limits except for a globulin of 3.9 grams and an albumin of 3 grams. Salt deprivation produced no untoward effects. Repeated true fasting blood sugar determinations were 33, 35, 37, and 24 milligrams percent while routine laboratory tests yielded values of 33, 38, 56, 44, 36, 64, 48, 72, and 85 milligrams percent on different occasions. The oral glucose tolerance test disclosed values of 48, 104, 135, 148, 96 and the intravenous test 55, 160, 117, 84, 48, 51 milligrams percent values at zero, 30, 60, 120, 180, and 240 minutes respectively. The insulin tolerance test, using 0.1 regular insulin per kilogram weight, showed a normal response within twenty minutes with a spontaneous return to the base line within an hour. Iodine-131 uptake was in the euthyroid range. The electrocardiogram was normal except for occasional premature ventricular contractions arising from a single focus. A two meter chest film was normal. Skull x-rays revealed mild generalized hyperostosis. A lumbar puncture disclosed normal manometrics, crystal clear fluid which contained six lymphocytes and normal sugar and protein values. A fasting electroencephalogram showed large amounts of high voltage sporadic, serial and paroxysmal one to three per second activity, diffuse, but with frontal and temporal accentuation, more so on the left. Hyper-



ventilation increased the amount of slow activity described. After intravenous glucose the delta activity disappeared almost completely, being restricted to four to six per second activity with moderate amplitude in the same distribution, but in much smaller amounts.

*Course:* After her initial recovery the patient's hospital stay was uneventful. An eighteen hour fast caused a lowering of the blood sugar level to twenty-seven milligrams percent and although the patient was tremulous and exhibited bizarre, automatic arm movements and seemed somewhat disoriented, she never lost consciousness. It was felt that the lack of correlation to fasting, the absence of typical night hunger or early morning confusion, as well as the spontaneous recovery from the three days stupor argued against a diagnosis of organic hyperinsulinism. The patient was discharged on a regular diet consisting of frequent small feedings.

She did well at home except for two episodes during which she "fell asleep for an hour or two." The patient was readmitted to the Gynecological Service in February 1951 because of vaginal bleeding. A diagnosis of endometrial carcinoma was made and the patient received radiotherapy treatments. During the course of these she endured several episodes of loss of contact with the environment, frothing at the mouth and manifested bizarre movements of the extremities. Fasting blood sugar determinations done during these attacks ranged between twenty-seven and sixty milligrams percent; and all symptoms could almost immediately be stopped by the intravenous administration of glucose. Repeat metabolic studies did not disclose any new findings. Unfortunately, further follow-up on this patient was lost.

#### TREATMENT

A diet high in carbohydrate, together with symptomatic therapy, is indicated in hepatogenic hypoglycemia. Frequent small feedings, particularly at bedtime, are suggested. Should the history and clinical findings suggest a pancreatic islet cell tumor, surgery is imperative because of the recurrence of symptoms which may prove more dangerous with advanced age, the development of obesity and the remote possibility of malignant disease. The post-operative prognosis is excellent although temporary diabetes may result (67, 68). Some patients whose clinical course suggested a pancreatic islet cell adenoma have been surgically explored and no tumor was found (69).

Some surgeons (70, 71, 76, 73, 74) believe that such patients who had responded poorly to a medical preoperative regimen, deserve a total or subtotal resection of the pancreas since such operations may remove tumors which might otherwise be missed. However, there is no universal agreement that hyperinsulinism can be remedied only if a sufficient amount of pancreatic tissue is removed. Chemical agents such as alloxan have fallen into disrepute because of their toxic manifestations (75, 76).

A brief explanation of the rationale of a high protein-low carbohydrate diet in spontaneous hypoglycemia seems in order. Protein during its metabolism yields approximately fifty percent of its weight as glucose. The slow rate at which this glucose is released into the blood stream is of advantage because it causes no post-prandial hypoglycemia (it avoids excessive secondary insulin secretion), it provides a source of glucose over a prolonged period of time and in severe cases it allows further restriction of dietary carbohydrates than could otherwise be effected (77, 78). Supplemental feedings in mid-morning, mid-afternoon and at bedtime should be added without increasing the total caloric intake, so as to prevent obesity which is frequently encountered in these patients. When hypo-

glycemia is more severe and the patient is unable to swallow, 0.5 to 1.0 milligram epinephrine in aqueous solution or in oil may be given subcutaneously along with ten to twenty grams glucose intravenously in the form of twenty-five or fifty percent glucose. In cases of intractable or frequently recurring hypoglycemia 1000 cc of five percent glucose in water may be given by elysis. In those patients it is essential also to give by gavage hourly feedings containing both glucose and milk until the symptoms have been relieved for several hours (32). Once the patient is able to take food by mouth small feedings at one or two hour intervals should be instituted. With few exceptions (28) the use of atropine to depress excess vagal tone is no longer advocated nor is the use of insulin before meals to prevent postprandial hypoglycemia.

#### SUMMARY

The differential diagnosis, medical and neurological features, pathology, basic physiology and treatment of spontaneous hypoglycemia are discussed. Two illustrative cases of idiopathic hypoglycemia are presented. It is suggested that Whipple's triad of diagnostic criteria be expanded to include characteristic, but rigidly defined, electroencephalographic findings.

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## PROFILE OF A SURGEON

### *Editor's Note:*

*A former House Surgeon of Dr. Arpad Gerster writes the following personalized story of a towering giant of yesterday. This initiates a series aimed at preserving the intimate details of the lives of our great men in their relationship to the Mount Sinai Hospital. Each author will be a man of maturity and stature who as a younger man knew his hero well, and generally served under him. No one now living, however eminent, will be included. It is hoped to preserve something of the feeling of those exciting times in which the reputation of the hospital was being built, by putting living flesh on the dry bones of medical reputation.*



Arpad Gerster, Attending Surgeon of the Mount Sinai Hospital from 1880 to 1915, was perhaps the most colorful personality on the staff of the hospital during the first century of its existence. Tall, strongly built, eloquent and positive in speech, firm in decisions, he dominated all his colleagues on the surgical staff. There was never any question of his authority on the First Surgical Division which he headed.

During the long years of his service at the hospital, the balance of power in the institution was maintained by an equally forceful and dominating character, the hospital's president, Mr. George Blumenthal. Both had high ideals of hospital service, yet they rarely saw eye to eye. Compromise was not in their nature. For this reason, Gerster never became president of the Medical Board, an office to which he rightly aspired as the most eminent leader on the clinical staff. To

avoid conflict between two such strong personalities, Abraham Jacobi was continued as president of the Medical Board and chairman of the Joint Conference Committee into his old age, long after he had retired from active duty as Pediatrician to the Hospital. As frequent arbiter between Gerster and Blumenthal, the institution was fortunate at that time in having the greatest hospital administrator of our time, Dr. Sigismund S. Goldwater.

These men created the environment into which I entered on July 1, 1905, as a frightened intern on the First Surgical Service of Dr. Gerster. Without any intention of following surgery as a career, I had chosen a surgical internship, which then meant two and a half years of training ending as house surgeon during the last six months. My ambition was to be an internist and, if possible, a clinical investigator but I preferred a surgical internship under Gerster because, rightly or wrongly, it seemed to offer better training for a beginner than did the medical service of that day. The ability to survive under such dominating and dogmatic personalities as Gerster, Blumenthal, Goldwater, Brettauer, Koplik, and Libman and, in the end, to be able to number them among one's close friends is perhaps an indication of the effectiveness of their training.

The life of an intern under Gerster was disciplined and arduous. As an example of the monastic character of the training, interns were not permitted to marry. Ward rounds began at 8 A.M. even though the staff may have been operating all night. On Sunday mornings the attending and house staff assembled at 7:50 on the fifth floor of the Administration Building and when Gerster emerged from the attendings' room at 8, the entire entourage followed in his wake as he walked rapidly down the hall and descended the steps leading to Ward T where rounds began. The discussions at each bedside were brisk and searching, often interspersed with ribald stories derived largely from his early days in Hungary. Then his bright Magyar face would light up and his blue eyes would sparkle with the joy of storytelling. Some of his stories would embarrass the prim little nurses. In fact, on several occasions, the superintendent of nurses, Miss Kirk, found it necessary to caution him, but with little, if any, permanent effect.

I recall an incident one Sunday morning on grand rounds when I cautiously suggested that a patient under discussion might possibly have syphilis—only to be ignored. When Gerster and his followers arrived at the bedside on the following Sunday, I could not refrain from bursting forth gleefully with the information that the patient had a 4-plus Wassermann, which was then a new test. Whereupon Gerster turned in my direction and bellowed: "Doctor-r-r, the man is an Austrian, isn't he? Every Austrian has a positive Wassermann!" Thus I was properly squelched.

On another occasion I was passing instruments at a complicated and delicate operation. Nurses were not entrusted by Gerster with this responsibility. Gerster called for a ligature. Hurriedly picking one up, I tried its tensile strength. It broke but nevertheless I handed him a broken piece. Putting his instruments down dramatically, he glared at me for a moment with fire in his eyes. Then, with unusual self-control, he sighed and muttered: "Inscrutable are the ways of the Instrumentarius. Just like God!"

Gerster was regarded as the father of aseptic surgery in this country. His historic treatise entitled *Rules of Aseptic and Antiseptic Surgery* was published in 1888. Many of the early surgeons of that era were numbered among his pupils, including William Mayo. I well remember Will Mayo visiting the hospital on several occasions to pay his respects to the "old man" and watch him operate.

Gerster's skill was particularly evident in plastic surgery, in which he took a special delight. If there was plastic work to be done, he would prefer to do it himself and leave the major abdominal or thoracic work to one of his young adjuncts, Albert Berg, Alexis Moschcowitz, and Edwin Beer. Under his strict discipline, some of the surgical pioneers of our day were developed—Howard Lilienthal in thoracic surgery, Charles A. Elsberg in neurosurgery, Albert A. Berg in gastrointestinal surgery, Alexis V. Moschcowitz in herniorraphy, and Edwin Beer in urological surgery.

Gerster's robust and often Rabelaisian humor was characteristic of his conversation in the hospital. On one occasion he proposed to graft a prepuce on a man's denuded index finger. Upon second thought, he refrained with the remark that he would not dare to place the poor man in jeopardy of being accused of sexual perversion every time he picked his teeth.

In contrast to his public performance, Gerster's conversation at home was always most circumspect. He adored his little wife and son Johnny. In her presence he was always the cultured gentleman. Their home was a center for music and the arts. Gerster's sister was the famous prima donna of the Budapest and Vienna Opera. A friend of Brahms before coming to this country, Gerster had a fine musical training. Two pianos always stood in the living room of his home on East 76th Street.

He was also a skillful etcher. One of his famous etchings pictured the hospital's first otologist, Dr. Emil Gruening (father of Ernest Gruening, recently Governor of Alaska) performing the first radical mastoid operation in this country. In the etching, the acromegalic face and hands of Gruening can be recognized and behind him, looking over his shoulder, is the leonine head of Jacobi.

His general scholarship included Greek and Latin and even some knowledge of classical Hebrew. In addition to possessing the polylinguistic abilities of most cultured Hungarians, and perhaps as overcompensation for being a gentile in a predominantly Jewish environment, Gerster acquired through the years a remarkable command of various Yiddish dialects. No member of the hospital staff, whatever his origin, could converse with newly arrived immigrants with such idiomatic facility and plausible accent. The staff was amused by these exhibitions, but the appreciation and confidence of sick patients were invariably captured by this astonishing familiarity with their provincial jargon.

I shall never forget a scene on the last grand rounds which he conducted. In honor of this occasion, some of us without his knowledge had assembled as many of his former pupils as possible from various parts of the country, some of whom he had not seen for years. At 8 that morning they were gathered on the fourth floor of the surgical pavilion, waiting to surprise him as he descended the stairs followed that day by an unusually large retinue of staff and distinguished visitors.



Briskly swinging around the corner of the staircase landing, he caught his first sight of the crowd of former pupils, old and young, gathered below him. He stopped suddenly. Looking down on them in silence for a moment, he threw up his hands as if in blessing and then, in a loud voice, he burst forth with the ancient Hebrew chant, Schmah Yisroel! Hear, O Israel! The applause of the crowd can be imagined.

Gerster's life and work are described in his autobiography, *Recollections of a New York Surgeon*. At the time he was writing these memoirs (1915), I was abroad on a sanitary expedition sent by the American Red Cross to fight an epidemic of typhus fever which was then raging in the Balkans. My temporary headquarters was in the town of Skoplje in southern Serbia. In his book, Gerster listed me among his pupils with characteristic humor as Baehr of Usküb, the ancient Turkish name for Skoplje. After my return to this country, he continued to give me that title, even after I settled down in 1919 in the practice of medicine just around the corner from his office. But to his dying day I am sure he never forgave me for deserting the noble profession of surgery.

GEORGE BAEHR

# ENCEPHALITIS WITH A CLINICAL PICTURE OF SCHIZOPHRENIA

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The diagnosis of schizophrenia is generally made on the basis of alterations in modes of communication in which the patient manifests delusions and hallucinations or expresses his feelings by attitudes of withdrawal from the environment or by using certain motor symbols as grimaces, posturing and mannerisms. Although metabolic and endocrine disturbances have been reported in schizophrenia no underlying pattern of brain dysfunction has been recognized. In the past few years we have observed a clinical picture of schizophrenia in six patients with encephalitis. The cases are being recorded because they illustrate the value of certain methods of neurological study in diagnosis and prognosis and contribute some ideas concerning the possible relationship of psychological and physiological factors in both the classical types of brain disease and schizophrenia.

## CASE REPORTS

### *Case 1*

A 30 year old man was admitted to The Mount Sinai Hospital on January 21, 1953. Three weeks previously he had had an upper respiratory infection associated with fever, headache, lethargy and vomiting. After two weeks he returned to work but could not continue because of persisting headache. Several days before admission he seemed confused and forgetful. He developed weakness of his left limbs and shortly after entering the hospital became stuporous. The past history was significant in that a similar episode had occurred 6 years previously. At that time he had had an upper respiratory infection with fever, headaches and vomiting, followed by a period of stupor lasting several days. On emerging from the stupor he had an acute psychotic episode consisting of rage and destructive violence necessitating the use of restraints for two weeks.

Neurological examination revealed a weakness of the left extremities. The patient was in a stuporous state and could not be roused to answer questions. A lumbar puncture yielded opalescent spinal fluid under increased pressure containing 384 wbc per cu mm of which 252 were polymorphs. Some gram positive diplococci were noted on a smear but no growth was obtained on culture. The EEG record showed diffuse bilateral slow wave activity more marked on the right side of the head. Because of the suspicion of a brain abscess, a craniotomy was performed with negative results. The illness was complicated by a pneumonic process in the left lower lobe. After three weeks in a stuporous state, the chest and spinal fluid findings cleared. He then showed a picture of marked apathy and withdrawal lasting for several weeks during which he appeared to sleep constantly and rarely answered questions. He generally spoke only to ask to go home and to demand food, having an enormous appetite.

Even after the patient was out of bed, he would ask to return to sleep. He remained incontinent of urine. He was disoriented for place, saying he was in Staten Island three blocks from his home and showed many reduplicative phenomena. He confabulated that he had nine children (actually two) and that he owned numerous automobiles all of which were parked at the front door. He fancied that he had a number of television sets some of which he had presented to the hospital as gifts. He misidentified people and confabulated having taken trips from the hospital, including one to another Mount Sinai Hospital in

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Chicago as the guest of the doctors. After his delusions cleared he still seemed lethargic, a state attributed by the patient and his wife to his desire to be home. He was discharged on March 13. At that time the neurological status was normal but he was still incontinent of urine unless someone were in his room to get him a urinal or take him to the bathroom.

*Pre-morbid Personality:* The patient was described by his wife and relatives as a childish person, depending on his wife for a great deal of help. She stated "I made a baby out of him". He would not go out without her except to engage in pigeon racing, his main avocation. He was an excellent eater at home, enjoying everything that his wife cooked but was critical and fussy when dining elsewhere. He frequently complained of constipation but had to be urged to take laxatives. His health had been good but he became panicky on the few occasions that his wife and children were ill. He avoided going to the dentist and his wife would have to make appointments for him and make certain that he kept them. The patient was easily depressed and his wife described a habit of sitting with his head down. He often felt a great deal better after "taking it out" on his wife or turning to his pigeons or woodworking. He had taken a great deal of pride in an automobile and spent much time in caring for it. When he purchased another car which proved unsatisfactory, he became worried and preoccupied and neglected the car.

The patient was very proud of his family, house and possessions. Prior to the birth of his two children he had been "crazy" about children, but after giving the first child a great deal of attention he showed interest only sporadically and had not wanted a second child. His own parents had been divorced and he had been raised by his father's relatives. As a child he would say that his mother was dead although in reality she was alive.

### *Case 2*

A 21 year old nurse was admitted to The Mount Sinai Hospital on September 8, 1951 in a drowsy state complaining of headache and stiff neck. One month previously, she had had an upper respiratory infection that had subsided in a few days without antibiotics. Three years before she had had an episode of motor overactivity, outbursts of laughter and depression and visual hallucinations, which was diagnosed as hysteria and treated with subshock insulin.

Examination showed the patient to be drowsy but resistive and negativistic. There was a mild left hemiparesis and a marked lack of response to all stimuli on the left side of the body suggesting an hysterical pattern. Kernig sign was mildly positive. There was a vertical nystagmus on upward gaze. Lumbar puncture yielded a clear fluid under normal pressure containing 8 lymphocytes per cu. mm. and a total protein content of 53 mgs. %. The EEG record showed diffuse bursts of 3-4 per second activity with right sided accentuation.

Shortly after admission the patient's temperature rose to 108 degrees F and for the next three weeks she had fever daily. On the third hospital day she was disoriented for place, denied being ill and expressed the delusion that she was pregnant. She was given intravenous sodium amytal during the period of hyperthermia. This produced an immediate temperature reduction to subnormal levels which persisted until the patient awakened.

Throughout her hospital stay the most striking aspect of the clinical picture was the patient's behavior. At times she seemed friendly and cooperative but more often she was sullen, suspicious and hostile. She resisted the administration of sodium amytal charging that it was being given for "improper" purposes. She told lewd jokes in inappropriate situations. Her behavior gradually improved and despite continuing elevations of temperature she was discharged on November 13, the neurologic signs having cleared.

She was apparently well until February 20, 1952 when she had another upper respiratory infection. After two or three days she developed headaches and dizziness and was admitted to the hospital in a hostile negativistic state. An EEG record showed diffuse bisynchronous slow (1.2 to 6 per second) activity. She went into a violent paranoid assaultive condition and was transferred to a mental hospital. The following day however, she appeared normal and was discharged. Since then there have been no psychotic episodes.

*Pre-morbid Personality:* The patient was described by her sister and roommate as having been an extremely rigid stubborn person. She had a great deal of drive, was ambitious and perfectionistic and had a great need to be "right" and gain the esteem and affection of others. She was not assertive, particularly with people in authority, and did not voice her feelings. The informants thought that she had never felt that she was as good as other people and greatly resented any indication that they thought so too. She seemed to distrust people and was "supersensitive" to any slight. She was often self-deprecatory and self-punishing to gain approval, frequently working extra hours and denying that she was tired after particularly exhausting work. She had a violent temper which she usually controlled and expressed resentment by silence and withdrawal.

She was very concerned and worrisome about her looks, hair and dress, being very self-conscious of her appearance. She would never go out unless perfectly clothed and was extremely clean and meticulous. In sexual matters she was regarded as prudish, refusing to undress in the presence of her roommate and becoming embarrassed if seen in a housecoat. She was a picky, fussy eater, especially fond of sweets.

The patient was the youngest of five children. Her alcoholic father, 40 years older than her mother, died when she was 18 months old. Until the age of four she had lived in numerous foster homes. At that time she and a sister went to live with a very strict and apparently over-conscientious woman who kept the patient until she entered nurses' training in her home town. Although no secret had been made of the family background, the patient had always insisted that her foster-mother was her true mother.

Following the second psychotic episode the patient was treated psychiatrically by one of us. She related that during the period preceding the first episode of illness she had been engaged in an unhappy love affair that occasioned a good deal of guilt and tension. She talked about the initial illness that had occurred three years previously. At that time she had also had an unfortunate affair with a married man and had been discharged from training school as a consequence of the situation. She said that her greatest fear in hospitalization had been that these facts would be discovered. In the course of treatment the patient became engaged to a man whom she subsequently married. When the therapist expressed some opinions in this matter contrary to those of the patient, she broke off contact without warning.

### Case 3

A 22 year old woman college student was admitted to The Mount Sinai Hospital on October 4, 1950. In August she had had an episode of headache, chills and fever diagnosed as infectious mononucleosis and treated with aureomyein. One week later changes in behavior appeared. She had auditory hallucinations, pressure of speech and flight of ideas and was admitted to a mental hospital in a state of excitement. She was given three electric shock treatments following which, because of a fever attributed to pneumonia, she was transferred to a general hospital where she was reported as being comatose for two weeks. A lumbar puncture yielded a fluid containing 400 lymphocytes per cu. mm.

On admission to this hospital she was resistive to examination keeping her eyes closed and picking at the bed clothes. She was incontinent of urine and feces and masturbated frequently. Her pupils were small and did not react to light or accommodation. There were bilateral Babinski signs and many irregular jerky movements of the face and extremities. She was disoriented for place, stating that she was in another hospital several blocks from her home. She stated that she had come to the hospital in order to have an abortion performed. She expressed fear that she would be given shock treatments. Lumbar puncture showed 130 lymphocytes per cu. mm. and a total protein content of 26 mgs%. An EEG record taken 12 days after admission showed much diffuse symmetrical delta activity with frequencies of from 1 to 6 per second and superimposed bursts. There were many stretches in the record when it was entirely flat, i.e. showing no electrical activity at all.

During the next three weeks she showed catatonic posturing and excitement. Speech contained many condensations and neologisms and she would sing fragments of songs. She



showed marked alterations in sexual behavior making advances to male and female personnel, but complained that she had no sexual feeling for her boy friend. She continued to be disoriented for place and time. During interviews she would keep her eyes closed although responding promptly to questions. She misnamed objects in paraphasic fashion, calling a wheel chair a "spinning wheel" for example. She stated that she was in the hospital for mononucleosis, on one occasion for "neuromocliosis" and that she had come for "reconstituscence".

Following this her behavior improved although her sexual behavior was still abnormal and she was demanding and petulant. She showed displacement on the face-hand test and was intermittently disoriented for place and time. After disorientation had cleared clinically the amytal test was positive. She talked obsessively about some hair on her chin, going home and getting married. She appeared more anxious and depressed. On one occasion she climbed out of her bed, emptied a flower pot and smeared mud over her body. She showed temporal reduplication, stating that one of the doctors had been a professor at her college. She had a course of seven electric shock treatments with apparent improvement. On December 12 she was presented before a conference. When her request to have her boyfriend attend was refused she went into a catatonic state for several hours. Her behavior became erratic. After long lucid periods she would perform such acts as undressing herself on the ward. Her EEG records had shown progressively less abnormality and one taken on December 5 showed only sleep patterns with bursts on hyperventilation. A final record on February 5, 1951 was normal.

*Pre-morbid Personality:* The account of the patient's previous behavior was given by her parents and a close girl friend. She was described as an intelligent, energetic, headstrong, impulsive person. She made friends and was considered an active, cheerful participant. She would be stimulated to great enthusiasms, insist on carrying out some impractical project immediately and then was apt to lose interest just as quickly and completely. She was artistic and interested in music and literature and expressed contempt for people who were not intellectual. She liked to think of herself as an independent, unconventional rebel. She was regarded as particularly irresponsible with money, being extremely generous and periodically extravagant. She had always had a fear of high places and bugs but otherwise her health had been good.

After entering college at 16, the patient had a number of highly romantic attachments. The first concerned a professor at college. The relationships were intense and stormy and apparently accompanied by much idealization on the patient's part. When one came to an unhappy end, it was followed by a new attachment equally intense. She seemed to adopt the interests of the particular boy; poetry, art, philosophy, etc. She would discuss these problems with her girl friends and was conventionally modest and secretive concerning sexual relations.

The patient was an only child. Her mother was described by the other informants as a very tense worrisome person who lived vicariously in her daughter. They had been very close and the patient had depended on the mother for many personal wants. For example she never washed her own clothes or cared for her room. The mother was overtly jealous of the patient's girl friends and critical of her dates. The patient was said to have confided a great deal in her mother. The patient however, expressed dissatisfaction with her home saying that her parents were too conventional and controlling. The father was an intellectual person who had been very indulgent to both his wife and daughter.

The year preceding the patient's illness appeared to have been a period of mounting tension. The mother had a nervous breakdown in which she had difficulty swallowing and could not be left alone. The patient left home and went to live with another family. A love affair came to an unhappy end and she developed another romance. In this affair she had had sexual relations and developed conflicts thereafter. She had also spent a great deal of money, placing her father in financial difficulties.

Following her discharge the patient was seen for psychotherapy by one of us until March 25, 1951. At this time nystagmus on upward gaze was still present and pupils were miotic but reactive. During this period she was completely oriented and not delusional in a clini-

cal sense but her behavior was characterized by poor judgment, irresponsibility, lethargy, neglect of her person, forgetfulness, confabulations and sexual aberrations. She was late and forgetful about appointments. At times she would be found curled up asleep in the waiting room. When in the therapeutic process a realistic appraisal of her interpersonal relations would be approached, she would react by obsessive rumination about what kind of a job she would get, long descriptions of her sexual experiences and complaints about her parents. In March she precipitately decided to go abroad to study music. She remained there for two years, under psychiatric treatment, and follow-up was kindly furnished us by Docteur Simone Blajain-Marcus. Over two years she made gradual improvement in approaching reality and after her return to America was able to work effectively.

#### *Case 4*

A 20 year old girl was admitted to The Mount Sinai Hospital on June 23, 1953. Eight days previously she had had an upper respiratory infection. During the next three days at home she was lethargic and irritable and ate a great deal, especially sweets. Following this it was noted that she was unusually quiet and had difficulty in following the thread of conversation. She returned to work but seemed vacant and forgetful. When examined by a doctor she became agitated and accused him of trying to make her crazy.

On admission her temperature was 104 degrees F. She was negativistic and withdrawn and when questioned would become mute and turn away from the examiner. The routine neurological examination was not contributory. Lumbar puncture was completely normal, the fluid containing no cells. The EEG record showed diffuse slow wave activity. An amytal test was positive for the existence of brain disease. After the intravenous administration of 0.4 grams the patient became disoriented for place. She located the hospital in the Bronx (near her home), referred to it as "Montefiore" and "Jefferson High School". She identified the examiners as people who "pick up and attack stray girls". Her behavior on the ward was characterized by withdrawal, slovenly dress and a huge appetite.

During the following week her behavior improved strikingly. An EEG record showed much less abnormality and an amytal test performed on July 3 was negative. She was communicative and alert and had an amnesia for the events of her illness. She was discharged on July 12. One week later she had an episode of confusion and agitation and admission to a mental hospital was recommended. The family took the patient home and her symptoms cleared in a few days. Since then she has shown no unusual behavior.

*Pre-morbid Personality:* The patient was described by her mother and maternal aunt as a rather withdrawn person with little drive. She had periods of talkativeness but frequently became moody and would retire to her room. She was considered to be very sensitive to criticism. She was much concerned with physical appearance. For the past two years she had talked about a rhinoplasty in obsessive fashion despite the fact that there seemed to be no obvious need for one. She went on diets sporadically and nibbled a good deal between meals. She was constipated, took many laxatives and attributed a tendency to overweight to improper bowel function. She was extremely neat and immaculate in her dress. The informants describe her as having been very aware of sexual connotations, being over-modest even at home and particularly shy and bashful with boys. She was unhappy over the loss of prestige involved in her poor social relationships. In her work as a bookkeeper she was conscientious and punctual but not ambitious or competitive. Her health had always been good and she disliked going to doctors. It had been difficult for example to get her to take the periodic physical examination required in school. The family felt that the greatest change that had recurred during her illness was that she had become so slovenly in her personal habits.

#### *Case 5*

A 25 year old nurse was admitted to The Mount Sinai Hospital on November 28, 1952 with an upper respiratory infection associated with headache. After nonspecific treatment she developed an urticarial rash which was treated with anti-histamines and ephedrine.

One week after admission she became restless, agitated and depressed and spoke of "feeling lost" and "having crazy ideas". Her abdomen was distended with urine and she expressed the delusion that she was pregnant. She accused the nurses of giving her a hypodermic to make her talk and worried that she had cancer and heart disease. Lumbar punctures on successive days showed cell counts of 43 and 380 lymphocytes per cu mm. She developed nystagmus on left lateral gaze, choreo-athetoid movements of the upper extremities and a right Babinski sign. She lapsed into a mute uncommunicative state and did not respond to painful stimuli. She kept her eyes closed and her teeth clenched. She showed a variety of stereotyped motor patterns, mainly rocking her head to and fro, grimacing and sucking of her lips, and made repeated unintelligible sounds with greatly exaggerated lip and mouth movements. She was incontinent of urine and feces, and had to be fed via nasal tube.

The patient continued in this state for three weeks maintaining a fever of from 102° to 104° following which improvement was noted. A lumbar puncture on December 13 showed only two lymphocytes. The EEG record of January 5, 1953 showed constant bisynchronous 1 to 3 per second activity over the frontal and temporal regions. She would talk to her nurses but remained silent in interviews with doctors, keeping her eyes closed or staring in the opposite direction. On several occasions she said that she was dead. When she began to respond more it was noted that she was disoriented for place saying that she was in her home city. She was also disoriented for time. There was little verbal denial of illness. Frequently, she would not answer questions about the nature of her illness. She remained incontinent of urine and feces, would call for her mother and had a demanding and paranoid attitude toward her nurses. She accused them of stealing a ring which belonged to her mother and of trying to kill her by making her get out of bed. She would strike and kick them and frequently scratched herself even though there were no remaining signs of her rash. She would call for food then refuse it. Her manner was that of a petulant child. She repeatedly misidentified hospital personnel as persons she had known previously (temporal reduplication). Though she steadily spoke more in interviews she would evade questions and tests by saying that they were silly and by complaining of being weak or sleepy, or of having an itch.

After becoming ambulatory her previous paranoid attitude was replaced by depression, many somatic complaints, and irritability. She had to be urged to take baths and was incontinent of urine on occasion. On February 8 she had a hallucinatory episode associated with agitation in which she thought the hospital was on fire. She was sedated with sodium amytal and on awakening was more lucid than she had been heretofore. She expressed the feeling that she had awakened from a dream and said that she remembered nothing of what had happened since the onset of her illness. In subsequent interviews she would begin by answering questions concerning the hospital and the identification of people correctly. She would then seem irritated and tired, misidentify people and ply the examiner with repeated stereotyped questions about her condition. She expressed many reduplicative and paraphasic misidentifications of persons. She thought one of the psychologists was an airplane stewardess and on other occasions an actress. She referred to her physiotherapist as "Nancy the exercise girl" and worried that her (Nancy's) hair was becoming straight and that she (Nancy) had lost weight. This of course was a displacement of the patient's concern about her own looks. The patient also voiced the idea that her (the patient's) mother had made Nancy's sweater. Another interesting expression of the altered relationship with the environment was a remark "We're all making asses of yourselves".

On March 5, the patient had improved sufficiently to go to a convalescent home. On reaching the place she had an acutely disturbed reaction consisting of bizarre posturing, mutism and apparent confusion. On being returned to the hospital this state cleared rapidly. She continued to be completely oriented and was discharged on March 20, 1953.

Following discharge the patient lived with her sister for several months. There she had periods of depression where she talked about killing herself and was noted as being forgetful. She seemed particularly perturbed before her menses. She did not return to work until

February 1954. Her adjustment has been fairly satisfactory with absences from duty when she does not feel like going in. In subsequent interviews she was affable, completely oriented and cooperative.

*Pre-morbid Personality:* The patient was described by her sisters and colleagues as a childish, impulsive, irresponsible person. She was the sixth in a family of seven children. Her father had died when she was seven and she was reported as very devoted to her mother. The mother was described as a strictly religious, hard working person despite a long standing illness related to her stomach and gall bladder. The patient entered nurses' training at 18 and was not considered to be industrious or conscientious. She was frequently late for duty, evaded work frequently giving illness as an excuse. When frustrated she had temper tantrums and would sulk and was treated by her supervisors much as if she were a mischievous child. She made friends easily but gave them up just as readily and seemed to make no close or serious relationships. She did things impulsively, rarely planning ahead. She had thought of becoming an airplane stewardess or an actress. She decided to enter nursing "just for the fun of it" and thought that she would only stay for a few months. During the affiliation at a mental hospital she became panicky and depressed and her friends would hold her back from apparent attempts to throw herself out of windows. She was quite concerned over her appearance and had a rhinoplasty performed several months before the present illness for a rather minor deformity. Although perceptive about looks and smells she was not orderly about her room and possessions. She was described as stubborn and rather secretive in some matters. For example she told no one about the rhinoplasty even after it had been performed. Her health had been good. She had a functional heart murmur about which she would joke. Since childhood, she had had a great fear of snakes.

An outstanding characteristic related by all of the informants was a ludic type of behavior\*. The patient seemed to think that "everything was a big game" and she loved to imitate people particularly if they had some unfortunate physical feature. She would laugh uncontrollably if someone had an accident. She had a habit of standing before a mirror and making faces. She loved to talk of how she had played "hookey" and fooled her teachers. As a child when scolded by her mother she would fall down and "play dead". She was a practical joker. A favorite was to complain of a stomach ache then make a noise with a cushion of passing wind. She liked to perform and a form of entertainment among the student nurses was to watch the patient awaken in the morning. She did this with many grimaces, noises and contortions. She was popular with boys and seemed to have a good time on dates. She would then like to relate the events of the evening to her friends in a comic fashion. She was religious in a naive sort of way. She would pray to pass an examination but not study for it.

### *Case 6*

A 26 year old housewife was admitted to The Mount Sinai Hospital on January 12, 1951. Following the birth of a child on September 20, 1951, she had complained of fatigue and apathy. The acute onset of her illness occurred on December 29 when she had an episode of headache, nausea and vomiting, dysarthria and numbness in her fingers. The symptoms returned on January 2 and she developed periods of confusion. She described peculiar perceptual disturbances in which the world seemed flat and unreal. She said that her husband looked different, being very fat and having leaves on his face and blue hair. She thought that the neighbors were having a party and was upset that she had not been invited. She had visual hallucinations in which she saw animals. On one occasion she stood in the shower pulling on her breasts and asking "why am I built so funny; what are these for?"

Examination on admission showed her to be in a bewildered state. She had catatonic posturings of the extremities. She was disoriented for time. She denied that there was any-

\* "Ludic" is the term applied by Jean Piaget to the imitative and pretending aspects of behavior in young children.



thing wrong with her (anosognosia) and believed that she was in the orphanage where she had spent her childhood. When asked her name she gave her maiden name. She made errors in the face-hand test involving the recognition of two simultaneously applied tactile stimuli; had difficulty distinguishing left from right and naming fingers and objects. A lumbar puncture yielded a clear fluid under an initial pressure of 170 mm. of water containing 191 wbc per cu mm., all lymphocytes. The EEG record showed diffuse symmetrical 4-6 per second activity with superimposed bursts.

The patient improved rapidly and examination four days after admission showed her to be completely oriented and aware of illness. She still had difficulties in left-right orientation and made errors in recategorizing as in spelling backward. The EEG record taken on January 23, showed numerous sleep patterns but a lesser degree of abnormality than in the first tracing. An amytal test was negative. By the time of her discharge on February 1, the entire mental status had returned to normal. The patient has been well since.

*Pre-morbid Personality:* The patient was described by her husband and an intimate friend as a calm, controlled rather detached person, rather shy and self depreciating. As a child her parents had quarreled a great deal which led to divorce and the patient had been raised in an orphanage. As an adolescent she was fat and felt herself to be unattractive. Prior to her marriage, two years before the illness, she had led a Bohemian sexual life with much drinking and the informants attributed this to her sense of inferiority.

She was said to be a talented artist but hampered in utilizing her ability because of lack of confidence in herself. In her work as secretary of an art association she had been responsible, energetic, perfectionistic and a good organizer. In other respects, such as taking care of the house she had spells of compulsive activity followed by neglect. After her marriage she seemed to worry about the management of her house.

The informants felt that the patient concealed a good deal of fear and insecurity in her relations with people which often seemed to be manifested as a lack of concern. She often seemed awkward and self conscious. She had a curious attitude about clothes being alternately indifferent and very interested and occupied.

Her health had always been good but she was frightened of doctors and hospitals. She was quite anxious early in her pregnancy, being afraid to visit the obstetrician and then finding it difficult to talk when she did get there. As the pregnancy progressed she seemed to react much more calmly. Following the birth of her child both informants felt she had been under a great deal of strain, particularly since the child was colicky and had feeding difficulties.

#### DISCUSSION

In each patient, the signs of brain involvement were preceded, by a period of from one to three weeks, by a nonspecific inflammatory process usually labelled as an upper respiratory infection. This and other features suggest that the subsequent illness was not a direct invasion of the nervous system by some virus or bacteria but rather that the cases fell into the group of the so-called post-infections encephalopathies. These are seen following the exanthemata, after vaccination or as a sequel to any infectious process. The mechanism is not known but the prevailing evidence is that there is a hyperergic reaction in which the nervous system has, during the initial infectious process, become sensitized. Whereas invasions by neurotropic viruses are usually associated with marked pleocytosis in the spinal fluid and affect grey matter more than white matter, the post-infections encephalopathies commonly manifest little or no cellular reaction in the spinal fluid. Thus one patient had no cells, another eight, another 43, while the highest cell count recorded was 490 white cells per cu. mm.

An attack does not produce immunity and the tendency of this type of en-

cephalopathy to recur has been noted (1-3). Two or more episodes occurred in three of the patients. Treatment with antibiotics did not appear to be of value. In four cases there was a history of a period of severe emotional stress preceding the onset of neural involvement. It is possible that physiological alterations associated with such tension may be an etiological factor in the hyperergic process. It may thus be of more than literary interest that in the "brain fever" so useful to nineteenth century novelists the onset of illness was typically preceded by some dramatic crisis in the heroine's life.

The other diagnostic methods, apart from the routine clinical examination that were of value were the EEG record, the face-hand test developed by M. B. Bender and associates (4), the recognition of certain patterns of disorientation for place, and the amytal test for brain disease introduced by the present authors with the collaboration of Dr. Leroy A. Sugarman (5-7). Abnormal EEG rhythms were noted in the five patients in whom records were obtained. In the cases of acute encephalitis of all types studied in this hospital by Strauss, Ostow and Greenstein (8), abnormal records were found in 37 of 55 patients whereas schizophrenic patients in their experience have normal records. It should be noted that in some of the patients, disturbances in behavior were still present after the pathological records had returned to a normal rhythm, or tended to recur in transient fashion in situations of stress.

The face-hand test is based on the recognition of a pattern of perceptual integration that occurs in transient fashion in normals, following general anesthesia, and persistently in children up to the age of five as well as in patients with brain disease. When two simultaneous tactile stimuli, are applied to the face and hand with the patient's eyes closed, he recognizes and locates accurately only one touch, usually that on the face. The other may be unperceived, displaced to another portion of the body, or in severe cases located out in space or on the examiner's body. In schizophrenic patients the face-hand test is normal or the pattern is not the orderly one seen in brain disease.

Disorientation for place was present on clinical examination in five of the six cases. In patients with brain disease, it is expressed in characteristic patterns (10, 11). These are called verbal identification, displacement and the confabulated journey. When the patient is asked where he is, the answer serves both as a means of locating himself and as the symbolic representation of some motivation or feeling, usually the need to be well. In verbal identification the patient names two places, one his correct whereabouts and the other false. Thus he may say he is in Mount Sinai Hospital and his apartment or may call the place Mount Sinai Restaurant or Hotel. Displacement may be shown in the patients statement that he is in a small hospital located close to his home or that he may name a hospital where he or a relative was once treated for some minor ailment. Or the patient may confabulate a journey out of the hospital as in Case 1 to another Mount Sinai in Chicago. In patients with brain disease there is almost always a preservation of a connection with reality. The patient usually states he is in a hospital or uses the name or some modification of the name of the hospital. His language serves both to identify his whereabouts and symbolize his feelings, as

was so well shown by a patient who, bored by rounds, referred to "Mount Schlepperman Hospital." Schizophrenic patients are rarely disoriented for place. When it occurs it is not as enduring or consistent nor does it follow the orderly pattern seen in patients with brain disease. The schizophrenic patient may not answer or he may give a cryptic response that is entirely symbolic of his motivation as "Hell" or "in my father's bowels".

The amytal test was developed from the observation that in certain states of altered brain function, these patterns of disorientation and a new symbolic organization, or language, for expressing the motivation to deny illness are used. Denial of such disabilities, for example as hemiplegia, blindness and the fact that a craniotomy has been performed is referred to as *anosognosia*, literally lack of knowledge of disease (9). The occurrence of these phenomena under ordinary hospital conditions is indicative of the existence of brain damage. When a patient with brain disease who appears oriented clinically is questioned under the influence of amytal sodium, those patterns of denial and disorientation may appear, particularly if the lesion is rapidly developing and deeply seated. In normal persons and schizophrenics such patterns are not elicited.

There are of course many useful psychological tests that help in differentiating patients with the usual forms of brain disease from schizophrenia. With disturbed patients however, they cannot be administered accurately so that the value of the procedures described is emphasized. Further when our patients had improved to the stage where such tests as the Rorschach could be administered, the records could not be differentiated from those of patients who had had schizophrenic episodes or other types of disturbed behavior. The distinguishing of these cases from schizophrenia however, is important both from the standpoints of prognosis and evaluation of therapeutic procedures.

Aside from types of behavior that served as points in differential diagnosis there were other modes of relationship with the environment that occur both in patients with brain disease and in those with schizophrenic reactions. They are being discussed because they illustrate interactions of motivational, perceptual and symbolic factors that appear in adaptation to many forms of stress. The understanding of these processes in patients with encephalitis and other forms of brain disease is germane to an appreciation of seemingly irrelevant behavior in schizophrenia.

Denial of illness was expressed in explicit verbal form in Cases 2 and 6 and is common in schizophrenic states. There its most frequent manifestation is the denial by the patient that he is mentally ill or that he has unsolved problems. While this is often attributed to "lack of insight," it is actually a form of defensive adaptation that occurred in this series of patients and some of its manifestations have been described in previous papers as paraphasia (12) and reduplication (13). In paraphasia the patient names an object in terms of some aspect of its structure or function. Thus in Case 3 the patient called a wheel chair a "spinning wheel". Another example previously cited was that of a patient who referred to a hypodermic needle as a "tiepin". The misnaming is not a random one, nor is it due to a generalized perceptual defect but it expresses some motiva-

tion, usually the need to be well. The objects that are commonly misnamed are those connected with illness and hospitalization such as a glass straw or a syringe. Objects of comparable complexity and familiarity are named correctly. The name given often indicates in addition, the patient's feelings about his situation as in the instance of an engineer with a severe disability after a head injury who called a syringe a "used-up old radio tube." The type of inter-relationship with the environment that occurs with the change in brain function is also illustrated by a patient who called the hospital "a curable place." Condensations and neologisms are also expressed. Thus in Case 3 the patient referred to her illness as "neuromocleosis" and said she had come to the hospital for "reconstituscence". The former, related to her original diagnosis of mononucleosis and the latter was probably a condensation of reconstitution and convalescence. Such terms are used by the patient in speaking of his main problem which is that of illness and incapacity.

Another change in symbolic expression that occur in patients with brain disease as well as in other stressful situations, is a use of the third or second person to express an idea pertaining to the self. Thus when an ill person is asked why he is in the hospital he may state that it is because his *wife* has headaches or "*They* say I'm sick." This changed language pattern was noted in the statement in Case 5 "we're all making asses out of yourselves".

There are also more expressions of motivations in material symbols dealing with parts of the body or in terms relating to sex, food, bowel functions, physical violence and death. Common slang furnishes ample illustrations. Such changes occur classically in paranoid states but the basic symbolic mechanisms are used by all persons in stressful situations.

These alterations in language are usually confined to areas of stress. While the stressful situation, in patients with brain disease most often concerns the illness and incapacity it may extend to other problems. Thus two patients had delusions concerning their fear of pregnancy while another (Case 6) denied being a mother. It is outside the scope of this paper to describe the various forms of schizophrenic language. It is likely that the many cryptic references, neologisms and peculiar syntax may be symbolic forms of adaptation integrated in comparable patterns.

Reduplication may occur in spatial, personal and temporal spheres. In reduplication for place, the patient confabulates that more than one place of the same name exists. Thus in Case 1 the patient talked about going to another Mount Sinai in Chicago. In reduplication for time the patient states that an event in the present has also occurred in the past. Thus in Case 3, the examiner was said to have been the patient's teacher in college. Personal reduplication is the confabulation that more than one person of the same or similar names exists. The manner in which the "extra" place time or person is differentiated from the original is symbolic of the particular motivation of the patient. Thus the "other" Mount Sinai is generally a hospital where serious operations are not performed or it is a branch for convalescents. Reduplication may express not only the need to deny illness as in the example cited but it may symbolize many other motiva-



tions. A depressed patient described in a previous paper thought that the patient in the next bed had been a doctor who had performed experiments in Nazi concentration camps. Reduplicative phenomena were especially prominent in Cases 1, 3, 4 and 5. In the last the patient misidentified other persons in ways that symbolized her *own* aspirations and fears, i.e. as "airplane stewardess" and someone who had lost weight and lost the curl in her hair. In reduplication the patient maintains a dual symbolic system, one portion being used for reference and the other for the expression of his feelings. A similar mechanism exists in the delusions and misidentifications of many schizophrenic persons.

In this group of patients there also appeared certain non-verbal forms of symbolic behavior. These included withdrawal, mutism and akinesia (Cases 1, 4, 5), overtly aggressive behavior (Case 2) and altered sexual activity (Cases 3 and 4). Just as the patient with explicit denial of illness is engaging in a symbolic portrayal of health, so these other types of behavior are symbolic representations of other biological processes, particularly relating to death, food, sex and violence. Such "imitations" are important adaptive mechanisms and are seen in drama, religious rituals, dreams, humor and the play of children as well as in schizophrenic reactions. Withdrawn states in severe forms are known as "akinetie mutism" (14). The patient is not in coma but appears "dead". He lies mute and motionless, usually does not eat and seems insensitive to pain (pain asymbolia). On the few occasions that the patient speaks he is apt to talk of being dead or buried in a cemetery. The behavior may thus be regarded as the symbolic "imitation" of death and suffering (15).

The account of the pre-morbid personality background indicated that there was a relationship between the patient's previous life experience and the modes of adaptation that appeared during the illness. The severity of the behavior disturbance is determined not only by the severity of the brain damage. Thus we have observed patients with comparable brain pathology where the alterations in behavior were confined to mild lethargy and depression. The patient tends to use the same symbolic elements that have been of particular importance in his past relationships. All six of our patients had had serious problems in interpersonal relationships. In Case 1, the patient had always tended to avoid and withdraw in stressful situations. In Case 3, where sexual alterations were prominent, the girl had previously attempted to achieve maturity and independence and express her resentments toward her mother, through hetero-sexual relationships. The effect of the brain disease is not to produce or to change the symbolic elements but rather to alter the pattern in which they are integrated, and maintain it in enduring fashion (16, 17).

It is important to point out that many of the symbolic mechanisms that have been described appear in normal persons, i.e. those without brain disease, under certain conditions. The behavior differs mainly in intensity and duration, in the degree of stereotypy, exclusiveness and repetitiveness and in terms of the particular environmental situation in which it appears. In dreams there is a delusional system containing the mechanisms of disorientation and reduplication. In the behavior of children ludic aspects, paraphasic and reduplicative

phenomena are prominent. Humor, prayer, proverb, poetry, myth and slang are examples of altered symbolic patterns. All are important devices for relief in stressful situations. It is likely that one of the attributes of normal brain function is the ability to use language simultaneously for purposes of reference and information and as a representation of individual feelings and motivations. Under stress the latter type of symbolic organization tends to prevail. It is probable that there is a constantly fluctuating threshold of brain function which furnishes the neural milieu integrating the various symbolic organizations. In this homeostatic process, adrenal cortical and other hormonal factors may play a role.

In patients with brain damage in whom delusions of denial, disorientation and reduplication are well established there is a conspicuous lack of anxiety. The type of brain pathology necessary for their maintenance is that which bilaterally involves the so-called centrencephalic or diffuse projection system. Thus these modes of behavior appear with diffuse or infiltrating or midline lesions rather than with superficially located or unilaterally circumscribed processes. The diffuse nature of the encephalopathic process fulfills this criterion adequately.

In conditions such as certain forms of encephalitis or brain injury where the pathology may clear rapidly, a period of agitated behavior not infrequently ensues. This is comparable to the "abstinence syndrome" which may appear when such drugs as morphine, barbiturates and alcohol are withdrawn suddenly from addicted individuals. It was such transitory episodes of agitation and panic often with hallucinations that so resembled schizophrenic behavior. At this stage the degree of brain dysfunction is not sufficient to maintain the orderly patterns of disorientation and denial nor has it improved to the point where a more complexly integrated system of relating to the environment can be established. One also may liken this to the period of anxiety that commonly attends the transition from sleeping to waking in anxious or depressed people. It is likely that the agitated state may represent an unsuccessful attempt to handle the stress of illness by restoring the symbolic delusional system that previously existed.

The schizophrenic person is under a great deal of stress in his interpersonal relationships. His problems, as a rule, deal not with physical illness and its implications but with felt inadequacies according to the ideals that he has acquired. He seeks constantly to avoid anxiety with some form of symbolic adaptation. Thus his delusion is often the symbolic representation of some person or event in terms of his particular motivation. The organization of the pattern depends on conditions of brain function. The nature of these conditions in physiological terms is as yet not understood, but one might expect that the relationship among neural factors and symbolic patterns and elements may involve some of the principles that we have outlined.

#### SUMMARY

1. A group of six cases of encephalitis with symptomatology suggestive of schizophrenia are presented.

2. The mechanism of the post-inflammatory types of encephalitis is discussed and the differential diagnosis from schizophrenia indicated.

3. Various forms of symbolic adaptation occurring in patients with brain disease are described. These include anosognosia, paraphasia, disorientation, reduplication and types of non-verbal symbolic representation. The relation of these to the milieu of brain function and factors in the pre-morbid personality determining the elements of the symbolic pattern are considered.

4. A theoretical formulation of the relation of psychological and physiological factors in schizophrenia, in the light of these observations is presented.

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# THE ANESTHETIC MANAGEMENT OF THE CARDIAC PATIENT WITH A NOTE ON INDUCED HYPOTENSION<sup>1, 2</sup>

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The past decade has witnessed a brilliant widening of the surgical horizon. This growth has its roots in the development of new surgical techniques, particularly of the cardiovascular system, in the investigations of the hemodynamics of heart disease and heart failure, in the advances of electrolyte and fluid balance, in antibiotic therapy and in the newer advances in anesthesiology. These collective advances have added to the daily operating lists in patients who decades ago were refused surgery because of complicating heart disease. Today it is rare to label a patient as "inoperable" because of some existing cardiac condition.

This paper concerns itself with these cardiac cases and will discuss the anesthetic management of the cardiac patient. It should not be construed as a review of the literature or a consensus of opinion. It represents the personal opinions of the author. We shall discuss briefly (1) the evaluation of the cardiac patient as an anesthetic risk, (2) the pertinent clinical features and cardiovascular effects of various anesthetic agents and techniques and (3) the anesthetic management of particular categories of cardiac patients. Some observations on the technique of induced hypotension will be made.

## EVALUATION OF THE CARDIAC PATIENT

When the final decision to operate on a cardiac patient is made, the evaluation of that patient as an operative and anesthetic risk is undertaken. This should be no mere academic exercise, but a serious practical search for answers to important questions. What are the calculated risks? What preoperative measures can diminish these risks? What anesthetic techniques and agents are safest for the patient and will afford the surgeon satisfactory working conditions? What therapeutic adjuvants, if any, should be used during the operation? What can the surgeon do to reduce the operative risk? These and other questions must be resolved by the internist, anesthesiologist and surgeon. While each has his specific role, they should work in close rapport and give freely to each other the benefit of their talents and experience.

The task of the internist is to establish the nature of the heart disease and, most important, to determine the functional capacity and reserve of the heart. The patient's margin of safety is determined by his cardiac reserve by which we mean the ability of the heart to tolerate work over and above its requirements at rest. A damaged heart that can carry an adequate circulation under normal daily conditions may be considered the equivalent of a normal heart. Anatomic diagnosis, size of the heart, murmurs, blood pressure and electrocardiographic

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findings are all secondary in importance to the cardiac reserve of the heart. If there is significant diminution in cardiac reserve, the internist must institute measures to increase that reserve. He must make decisions on the problems of bed rest, digitalization, the use of antiarrhythmic drugs (e.g. quinidine, procaine amide), mercurial diuretics and coronary vasodilators. The goal of the internist should be to present the anesthesiologist with a patient who has reached his maximum in cardiac efficiency and to convey to the anesthesiologist a clear picture of the patient's anatomic diagnosis, cardiac reserve and preoperative preparation.

It is the anesthesiologist's task to preserve and sustain the patient's cardiac efficiency and to do nothing that might reduce it to the point of danger. In other words, he must decide upon an anesthetic technique—not one most convenient for himself, nor one easiest for the surgeon, but one that is safest for the patient. A safe anesthesia will avoid (a) emotional excitement before and during surgery, (b) excessive physical exertion during anesthesia, (c) hypoxia, (d) hypercapnea, (e) marked depression or elevation of arterial and venous pressures, (f) diminished coronary blood flow and (g) changes in the irritability of the cardiac muscle. The internist should not attempt to dictate, as he sometimes does, the anesthetic technique. Such an attempt is illogical for the internist is unable to evaluate two very important sets of factors which always influence the choice of anesthesia, namely, (1) those factors which are related to the needs of the surgeon, based on the operation to be performed and on the habits and abilities of the surgeon and (2) those factors which are dependent on the experience and talents of the anesthesiologist. These two sets of factors are most apparent to the anesthesiologist. It would be sad, indeed, if the internist insisted upon an anesthetic technique with which the anesthesiologist was not too well versed. Whatever the theoretical considerations, it is imperative that the anesthesiologist be permitted to use a technique of his own choice; naturally, it will be a technique in which he is most experienced and adept.

One of the anesthesiologist's important duties is the preoperative visit to the patient. He must convey to and instill in the patient a sense of full confidence in the outcome of the operation. He reviews the internist's evaluation of the patient's cardiac reserve. He studies the patient's physical habitus to determine the possibilities of respiratory difficulties, as in the short-necked, thick-chested individual. He reviews the patient's anesthesia history, if any, and attempts to elicit previous responses to anesthetic agents and premedicant drugs.

While the essential role of the surgeon is to perform the operation, the pattern of this performance is crucial. Gentle handling of tissues, minimal visceral traction and elimination of unnecessary manipulations and loss of time are imperative. The nature and extent of the operation are the surgeon's responsibility. An appreciation of the patient's condition and the anesthesiologist's problems adds to the effective team work and the patient's welfare. The surgeon who demands profound, cadaveric relaxation in these patients does not help. The anesthesiologist who accedes to such demands fails in his obligations to the patient.

## ANESTHETIC TECHNIQUES AND AGENTS

*1. General Anesthesia*

This technique presents two hazards to the cardiac patient which merit emphasis; these are hypoxia and respiratory acidosis. The deleterious cardiac effects of hypoxia, whether due to respiratory obstruction, underventilation, overdosage with preanesthetic drugs and anesthetic agents or to muscle relaxants are too well known to justify further belaboring. Respiratory acidosis with an elevated  $p\text{CO}_2$  and lowered pH has been recognized of late as a significant hazard which may occur with any general anesthetic agent if total ventilation is reduced. It will be recalled that arterial pH and  $p\text{CO}_2$ , in patients with an intact thorax, are a close function of total ventilation. There is considerable evidence that elevated  $p\text{CO}_2$  during anesthesia may produce electrocardiographic effects as nodal rhythms, ectopic beats and depression of S-T segment. Other cardiac effects of increased  $p\text{CO}_2$  are decreased contractile force of the heart, increased cardiac irritability, and increased response of the heart to vagal stimulation. Sudden reduction of an elevated  $p\text{CO}_2$  predisposes to ventricular fibrillation. Where arterial  $\text{CO}_2$  has been permitted to rise during anesthesia, sharp falls in blood pressure may occur in the immediate postoperative period. This hypotension has been labelled "cyclopropane shock"; this is a misnomer because it may occur with any general anesthetic agent.

(A) Di-ethyl ether: This is an extremely potent anesthetic agent with a wide margin of safety. Surgical anesthesia can be attained with 4-6% ether concentration permitting the patient to receive about 95% oxygen concentration. Ether is remarkably free of untoward cardiovascular effects when administered skillfully. In the absence of hypoxia and undue depth of anesthesia, ether has little effect on the contractile force of the heart and on blood pressure. It does not sensitize the cardiac automatic tissues. Cardiac arrhythmias which appear during ether anesthesia are of a benign nature, almost always atrial and nodal in origin and rarely from the ventricle. Deep ether anesthesia will lead to diminished contractile force of the heart and fall in blood pressure. Ether has the disadvantages of slow induction, increased tracheo-bronchial secretions and diminished liver and renal function. Such disadvantages are outweighed heavily by the almost negligible effects of ether on the heart. Ether is a tremendously versatile and useful agent for the cardiac patient.

(B) Nitrous oxide: This anesthetic gas is free of any deleterious cardiac effects when administered with adequate amounts of oxygen. However, it lacks anesthetic potency and cannot be used alone for major operations. It can be combined with other agents, such as pentothal, and used successfully in superficial operative procedures and where muscular relaxation is not needed.

(C) Ethylene: Like nitrous oxide, this anesthetic gas has no untoward cardiovascular effects when unaccompanied by hypoxia. Because it is slightly more potent than nitrous oxide, ethylene can affect surgical anesthesia without hypoxia in well premedicated and older patients. The incidence of cardiac arrhythmias during ethylene anesthesia is the lowest of all inhalation agents. It does not

sensitize the cardiac automatic tissues. In our hospital it is used extensively in cardiac patients either alone or in combination with ether.

(D) Cyclopropane: This is the most potent of all anesthetic gases. It affords a rapid and smooth induction, affects surgical anesthesia in relatively low concentrations and can be administered with high concentrations of oxygen. It exerts little effect on liver and kidney function. Its cardiac effects are significant. Cyclopropane produces two types of disturbance in cardiac rate and rhythm. The first type consists of slow rhythms resulting from the parasympathomimetic action of cyclopropane and an increased vagal tone; these are not of clinical importance. The second type consists of rapid rhythms which result from increased myocardial irritability, a direct effect of cyclopropane. These rapid rhythms are apt to occur in deeper planes of anesthesia and are of ventricular origin; these include premature contractions, multiple focus ventricular tachycardia and, rarely, ventricular fibrillation. These rhythms can be precipitated or enhanced by sympathomimetic drugs, hypoxia, hypercapnea, fear and pain. Their incidence may be reduced sharply by the addition of small amounts of ether to the anesthetic mixture; this is a common practice at this hospital. Procaine, procaine amide, quinidine and dibenamine have been used as a prophylaxis against arrhythmias under cyclopropane. We do not use these drugs. When we cannot terminate a serious cyclopropane arrhythmia by lightening the anesthesia and adding small amounts of ether, we prefer to change our anesthetic agent entirely. It is best to avoid cyclopropane where there is evidence of increased myocardial irritability, conduction defects and cardiac arrhythmias. In the absence of such disturbances, there is no contraindication to the use of cyclopropane in cardiac patients if administered by a skilled anesthesiologist.

There are other circulatory effects of cyclopropane. These include a rise in arterial blood pressure, a rise in central venous and right auricular pressure, decreased arteriovenous oxygen difference and post-anesthetic hypotension. The mechanism and significance of these effects are not fully understood.

(E) Chloroform and ethyl chloride are contraindicated in cardiac patients. Both drugs are potent myocardial depressants.

(F) Intravenous barbiturates: Pentothal, evipal and surital are ultrashort acting drugs which afford a rapid, smooth and pleasant induction. In the absence of overdosage these drugs have little or no effect on the cardiovascular system. However, these agents are not true anesthetics; they are hypnotics and should not be utilized for operative procedures which require relaxation but should be confined to superficial and short procedures. Large doses will lead to respiratory and myocardial depression and prolonged postoperative sleep. In the cardiac patient an intravenous barbiturate is happily suited for a quiet induction, with the avoidance of struggling, breath-holding and undue emotional strain. In combination with nitrous oxide and ethylene, these drugs are well suited for the cardiac patient in superficial and relatively short procedures. Where regional or spinal anesthesia is employed in the cardiac patient an intravenous drip of 0.1-0.2% pentothal or surital will allay apprehension and provide a desired and pleasant sleep throughout the operative procedure.

## *2. Regional Anesthesia*

(A) Local infiltration and field block: If we exclude the rare convulsant and depressant cardiovascular effects of the local anesthetic drugs, these agents are remarkably safe for the cardiac patient. They have no untoward effects on cardiac, liver and renal function. These anesthesia techniques are sadly neglected in the cardiac patient and should be used more extensively. A wide objection to regional block techniques is that there is too much emotional stress and strain for a patient with limited cardiac reserve. Our experience indicates that this is not completely true if the following criteria are met: (a) good rapport between the patient and anesthesiologist, (b) careful selection of the patient and the operation, (c) sufficient preanesthetic medication and supplementation of this during the operation whenever necessary, (d) meticulous performance of the block technique and (e) exquisitely gentle handling of tissues by the surgeon. Another objection to local anesthesia is that it does not readily permit intra-abdominal procedures: this is true if local anesthesia is not supplemented with either intravenous barbiturates or light inhalation anesthesia. However, if combined with some form of inhalation or intravenous anesthesia, a wide variety of intra-abdominal operations is feasible.

(B) *Spinal Anesthesia*. This technique may produce significant hemodynamic effects which are attributed to sympathetic blockade and interruption of vaso-constrictor impulses to the arteriolar bed. There is decreased peripheral resistance and pooling of blood. This results in diminished venous return to the heart, decreased cardiac output and the accompanying risks of lowered coronary blood flow and myocardial anoxia. The extent of these hemodynamic alterations is in direct proportion to the height of the spinal block. For clinical purposes we distinguish between low and high spinal analgesia. In the former, the level of anesthesia is confined, for the most part, to the lumbosacral dermatomes; this produces little circulatory disturbance and permits us to use low spinals in cardiac patients for surgery of the lower extremity, perineum, rectum and bladder. High spinals, which are used in intra-abdominal surgery, have anesthesia levels up to D6 and D4 and produce significant physiological disturbances. These may prove to be a grave burden in the hypertensive and arteriosclerotic patient and in any cardiac patient in shock or with an associated decreased circulating blood volume.

## ANESTHETIC MANAGEMENT

### *Rheumatic Heart Disease*

The patient with rheumatic valvular disease, if well compensated, presents no significant hazards and accepts any or all of the various anesthetic techniques. It is the patient with a tight and limiting mitral stenosis who concerns us for this patient is apt to have a fixed, very low cardiac output and a pulmonary hypertension. Under physical or emotional stress pulmonary edema can easily result from a further elevation in pulmonary blood pressure. Hypoxia and hypercapnea will have the same effect. For superficial operations, regional anesthesia is preferred; supplementation with a dilute pentothal infusion or nitrous oxide is very



useful. In lower extremity, perineal and lower abdominal wall surgery, spinal is preferred; vigilance against sharp falls in blood pressure must be exercised. Intra-abdominal operations are best handled with general anesthesia; our choice of agents are pentothal for induction and ethylene-ether for maintenance. These patients tolerate general anesthesia and intra-abdominal surgery very well if the induction is smooth and quiet, if very light anesthesia is maintained and if ventilation is satisfactory.

### *Coronary Artery Disease*

These patients constitute perhaps the most serious of the cardiac groups because of their decreased coronary blood flow and diminished work tolerance. They are tense patients, apprehensive and very "heart conscious". It is imperative that these patients be free of unnecessary emotional burdens and that their hearts be spared physiological excesses. Whatever anesthetic technique is used, it is important that a basis for security and confidence be established between the patient and anesthesiologist. For superficial operations and procedures about the perineum and lower extremity, we prefer some form of regional block or low spinal analgesia, providing this is accompanied by preanesthetic medication to the point of sleep or this be supplemented by intravenous barbiturates. For intra-abdominal procedures, general anesthesia is our choice of technique. While we prefer ethylene-ether and cyclopropane-ether, it does not matter too much which agents are used if the following criteria are met: (1) effective preanesthetic sedation, (2) smooth induction, (3) light plane of anesthesia, (4) high concentration of oxygen in breathing bag, (5) avoidance of hypercapnia and (6) maintenance of blood pressure. When these criteria are met, the vast majority of these patients are managed with success. The question is raised not infrequently as to whether the presence of chronic auricular fibrillation affects the choice of agent or technique. On the whole it does not, except perhaps to eliminate cyclopropane. It is of interest that chronic auricular fibrillation does not increase the operative risk if the ventricular rate is below 100 and if there is no recent episode of congestive heart failure.

The existence of a conduction defect does not alter the anesthetic management, except to eliminate cyclopropane, but it does alter the prognosis. These patients are poorer surgical and anesthetic risks because of their advanced degenerative myocardial changes.

On rare occasions, we are confronted with a surgical patient in whom there is a fresh, or very recent myocardial infarction. These cases are best handled with some form of general anesthesia with meticulous care and attention to the previously listed six criteria for good anesthesia in patients with coronary artery disease. These patients tolerate the operation and anesthesia surprisingly well.

### HYPERTENSIVE CARDIOVASCULAR DISEASE AND INDUCED HYPOTENSION

The patient with benign or uncomplicated hypertension presents little problem to the anesthesiologist. These patients will accept all agents and techniques with the possible exception of high spinal anesthesia. Any accompanying cerebrovascular disease and impairment of renal or cardiac function increase the risk

of anesthesia and surgery. The primary aim of the anesthetic technique is to avoid drastic falls in blood pressure which may diminish seriously cerebral, coronary or renal blood flow and produce local tissue hypoxia. We prefer to avoid spinal anesthesia in these patients and use general anesthesia. It should be remembered that deep general anesthesia, whether with pentothal or ether, will depress blood pressure and can match spinal anesthesia in its hypotensive effect.

I must confess that today I am less sure of the anesthetic management of hypertensive patients than I was several years ago. This uncertainty is born of the recent introduction of hypotensive anesthesia or induced hypotension, a technique in which arterial blood pressure is intentionally reduced to levels of 60–80 mm Hg during surgery. Logic has led us to emphasize the need for maintaining as closely as possible the physiologic status quo. It is somewhat disconcerting to observe the work on induced hypotension which is truly a form of “physiological trespassing”.

Induced hypotension is used to attain a bloodless operative field, to minimize blood loss and to shorten the operative time. The methods of inducing hypotension include spinal anesthesia, epidural anesthesia, arteriotomy with provision for prompt reinfusion of the blood and various ganglion blocking agents, such as hexamethonium, arfonad and pendiomide. Arfonad and pendiomide are short-acting, controllable, ganglion blocking drugs. We prefer arfonad and pendiomide to other drugs or methods of inducing hypotension. These are administered as a continuous intravenous drip in a 0.1% concentration.

The indications for induced hypotension are controversial and vary from clinic to clinic. A conservative approach in this question would list the following indications:

1. Operations in which massive hemorrhage may occur: spleno-renal shunts, procedures for extremely vascular tumors, evisceration techniques.
2. Vascular surgery: as in aortic transplants and correction of coarctation of the aorta.
3. Neurosurgery: as in intracranial aneurysms and highly vascular tumors e.g. meningiomas.

The contraindications are more precise; these include:

1. Coronary artery disease or severe heart disease
2. Hepatic or renal insufficiency
3. Atherosclerosis
4. Severe anemia and diminished blood volume
5. Shock, whatever the cause
6. Degenerative central nervous system disease

We utilize induced hypotension only in selected neurosurgical cases where we feel that the operation would be technically impossible or unusually protracted without a bloodless field; only good risk cases are chosen. Our results have been excellent. Ours is a cautious approach based on a desire to await further clarification of the effects of induced hypotension on coronary blood flow, the mechanical efficiency of the heart, renal and hepatic function, cerebral blood flow, tissue respiration and operative morbidity and mortality. There is evidence that with

induced hypotension there is a statistically significant increase in operative morbidity and mortality when systolic blood pressure falls below 80 mm of mercury for a protracted period of time. Cerebral thrombosis, cardiac arrest, circulatory collapse and reactionary hemorrhage appear to be the more common complications.

The basic question that must be resolved is whether the calculated risks in this technique are justified and outweighed by the alleged benefits or advantages.

### *Congestive Heart Failure*

There are very infrequent surgical emergencies in which the patient is in congestive heart failure. Such cases are practically always major surgical conditions as peripheral embolization, acute gastrointestinal bleeding and intestinal obstruction. Fortunately, few cases are so urgent that they cannot await definitive treatment of the heart failure.

We feel it important that regional and low spinal anesthesia be used as much as possible in these cases, with emphasis on the former. There are theoretical considerations which suggest that spinal is an ideal anesthesia for the patient in failure; there is evidence that the extensive sympathetic block under spinal with its resulting vasodilatation produces a "bloodless phlebotomy" and serves as a therapeutic measure. In practice, the picture is somewhat different, for too often the hypotension accompanying the spinal anesthesia appears to aggravate the heart failure. Low spinals appear to be well tolerated by these patients; thus they are useful in lower extremity and perineal work. We avoid high spinals. If regional anesthesia is not feasible for intra-abdominal manipulations, some form of inhalation anesthesia is employed with particular emphasis on very light anesthesia, high oxygen concentration and adequate ventilation. Intravenous fluid therapy is interdicted or sharply restricted. Patients should be maintained in Fowler's position during the operation.

### CONCLUSION

We have touched briefly on the evaluation of the cardiac patient as an anesthetic risk, the significant cardiovascular effects of various anesthetic agents and techniques, and the management of specific cardiac groups. Two last observations are pertinent. There is no single anesthetic technique or agent which is always best for the cardiac patient. Any one of all possible choices may be the best under particular circumstances. Also an anesthetic drug is made good or bad by the anesthesiologist administering that agent. As aptly put by a colleague, "do not classify anesthetics as safe and dangerous, but remember that there are safe and dangerous anesthetists."

# THE TECHNIQUE OF THE SECRETIN TEST: NORMAL RANGES<sup>1</sup>

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The imminent release by the Eli Lilly Co. of a Secretin preparation for general use will doubtless result in the establishment in many clinics of laboratories in which the secretin test will be performed for diagnostic and investigative studies. It seems pertinent, at this time, to describe in detail the exact technique of the test and to present the volume, bicarbonate, and enzyme ranges derived statistically from the data of studies performed with the Lilly Secretin<sup>2</sup> on patients without pancreatic disease.

## TECHNIQUE

The secretin test is performed upon patients in the fasting state. It is best done early in the morning so that the collection of specimens and their analysis can be accomplished the same day. The patients are instructed not to take food following the evening meal on the night prior to study. This is of importance whenever there is any evidence of pyloric dysfunction, since retained food particles in the stomach and duodenum not only invalidate the results of study by the induction of endogenous secretin but also may become impacted in the tube and therefore make quantitative drainage of the stomach and duodenum impossible.

A large bore double lumened gastroduodenal tube is used. To be of sufficient caliber to assure constant open drainage, this tube is too large to be passed intranasally and hence it must be introduced orally. No water need be given with the passage of the tube; if this be done quickly, the maximum discomfort is over within 2-3 minutes. Pharyngeal cocaineization is not only unnecessary but, in my experience, increases the difficulty of duodenal intubation. Some of the cocaine is swallowed and appears to interfere with gastric motility and with pyloric relaxation. Cocainization was resorted to in five hypersensitive patients among 1500 secretin tests, but never with convincing efficacy.

It is imperative that the collection tube be radiopaque, for, once it is passed, the patient should immediately be fluoroscoped. It is a waste of precious time to attempt to intubate without the fluoroscope. First, should the tube become coiled or should its tip be directed back towards the cardia, the patient might lie on his right side for hours without passage. Second, it is impossible to accurately position such a tube within the duodenum without fluoroscopy.

During the initial fluoroscopy, any kink in the tube is undone by withdrawing it and the tip is directed towards the pylorus by manipulation if necessary. Then, while the patient is still being fluoroscoped, the tube is slowly advanced until

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<sup>2</sup> The Secretin used in this study was donated by Dr. James B. Hammond of the Eli Lilly Co.



its tip reaches the pylorus. Often this will result in immediate passage of the tube into the duodenum. Occasionally, pressure on the duodenum backwards and to the right may push the tube into the duodenum. Once the latter has been entered, the tube is advanced until its tip is at the ligament of Treitz. In the stomach, the tube should lie along the lesser curvature. In this position, all the openings of the longer segment will be in the duodenum, and those of the shorter segment in the stomach. Excess tube in the stomach is to be avoided since it permits progression into the small intestines during the test procedure.

If the tube does not enter the duodenum spontaneously or with manipulation during the initial fluoroscopy, it is best to leave it in the pyloric segment and to place the patient in bed, either flat or lying on the right side. Both outlets of the tube are put under gentle suction and the patient is allowed to remain thus until bile appears in the drainage. This heralds passage and usually occurs within 30 minutes. Then the patient is returned to X ray for final fluoroscopic positioning of the tube. In patients with marked cascading or "J" shaped stomachs, it is of advantage to use both horizontal and vertical fluoroscopy, but this is not essential.

Duodenal intubation, when performed in the manner described, should not take longer than 45 minutes and should average about 30 minutes. When it is accomplished, both outlets of the tube are connected to flasks, and these to a gentle suction such as a Gomco pump (high suction at 120 mm H<sub>2</sub>O). Drainage is permitted to continue until a non-turbid, alkaline secretion without or with bile is obtained from the duodenal outlet. Then a control collection period of 10-20 minutes is taken. This is done not only to allow for analysis of the unstimulated duodenal juice but also to eliminate the secretory effects of secretin endogenously induced by the hydrochloric acid which may have been present previously in the duodenum.

After the control period, it has been customary to inject a standard submaximal dose of secretin, 1.0 clinical units per kilogram of body weight. The secretin extract is provided in lyophilized powder and can be dissolved readily in 5 or 10 ml. of distilled water. It is advisable to perform an intradermal or conjunctival sensitivity test to avoid possible allergic reactions. In over 900 tests with this preparation, we have encountered no sensitivity and no other deleterious side reaction, but these, and even anaphylactic shock, have been reported with other secretins. The solution of secretin is injected intravenously, slowly, with barbitage, and over a period of at least two minutes.

Following the administration of secretin, gastric and duodenal drainages are collected simultaneously in divided samples for 30, 60, or 80 minutes. Ten or twenty minute collection periods may be used. For precise investigative physiological studies, the 80 minute collection time using 10 minute samples should be employed (1) for this is the interval during which the submaximal stimulus applied to the pancreas is completely dissipated. There is good experimental evidence that for diagnostic purposes 60 minutes (2-4) and perhaps even briefer collections may be adequate (5).

The patient requires no especial attention during the collection of samples.

Where laboratory facilities are at hand, some of the analysis of specimens may be done during this collection. Whenever a sample flask is changed at the end of a collection period, it is advisable to inject about 10 ml. of air through each tube outlet. This prevents clogging of the tube by mucous and/or sealing of the distal orifices by adherent mucosa.

It would be ideal following the completion of the test to check the position of the gastroduodenal tube fluoroscopically prior to its withdrawal. This is mandatory in patients in whom obvious deficient flow is obtained, for displacement of the tube during the test is possible. Five such cases have been observed in our series. Repositioning of the tube and a second administration of secretin yielded a normal response in each instance.

#### ANALYTIC METHODS

The gastric specimens are examined for volume, pH (acidity), biliary pigment concentration (icterus index), and guaiac reaction. Often a gastric analysis may be of diagnostic importance in patients studied with the secretin test. If sufficient information is not obtained during the test procedure, histamine or histalog may be administered following it.

The pH is conveniently determined by hydron paper. Free and total acid may be obtained by direct titration. Volume, pH, and biliary pigment concentration are important indices of regurgitation of duodenal contents into the stomach. This should not occur with proper intubation. Regurgitation is heralded by sudden increases in gastric volume, the appearance of bile in the gastric specimens, and sudden increases in pH. Small regurgitations into the stomach need not invalidate the secretin test data.

The following determinations are made on the duodenal fractions: pH, volume, bicarbonate concentration, enzyme concentration, icterus index, guaiac reaction, and cytology. The duodenal pH is a useful index of gastric contamination of the duodenal contents. While the obverse, as previously noted, is of minor importance, the entrance of gastric acid into the duodenum invalidates the secretin test because it causes a neutralization of pancreatic bicarbonate secretion, an inactivation of the pancreatic enzymes, and also incites the elaboration of endogenous secretin. Fluctuation of the pH values and/or a drop to levels below 7.0 indicates gastric contamination. Such is seen about once in every two hundred patients and usually implies movement of the tube. The tube should be repositioned and the test must be repeated.

The guaiac reaction of the gastric and duodenal specimens may be of importance in pinpointing the source of obscure gastrointestinal bleeding. Guaiac positive duodenal drainage may imply an intrinsic lesion of the duodenum, the biliary tract, or the pancreas. Bleeding from trauma occasioned by the passage of the tube rarely occurs and then only in patients who retch violently. This type of bleeding is gross and does not persist beyond the initial collection periods.

Cytologic study of the duodenal specimens should be done on the fresh samples preferably the control and the first collection following secretin. The biliary and

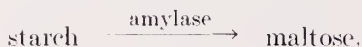
pancreatic flow following the administration of the hormone flush neoplastic cells into the duodenum. The sediment is smeared on a slide, fixed in alcohol, and studied microscopically according to the techniques described by Lemon (6) and others (7, 8).

The volume, bicarbonate, and enzyme secretion characterize the pancreatic response to secretin. Bicarbonate concentration can be determined by titration or more simply by a van Slyke apparatus. Either a volumetric or manometric gasometer may be used. The former has the distinct advantage of rapidity in determination of  $\text{CO}_2$  content in fluids containing minimal amounts of protein. Bicarbonate concentration can be done with this apparatus as quickly as the specimens are obtained, which obviates the collection of duodenal drainage under oil as has been advocated by some to prevent the loss of bicarbonate upon standing. As a matter of fact, even if the specimens are exposed to air at room temperature for several hours, serial determinations will reveal little if any significant change in the bicarbonate concentration.

The enzyme concentrations may be done upon each collected specimen or upon an aliquot of the combined total drainage. Since the diagnostic significance of enzyme concentration, per se, is of little diagnostic importance, and since the statistical scatter of data in normal patients is great enough to prevent the derivation of convenient normal ranges (1), enzyme determinations of each specimen are not necessary except for research problems.

Determinations of the concentration of the pancreatic enzymes amylase, trypsin, and lipase are required only in investigative studies. In accordance with the principle of parallelism of secretion of enzymes (9), only amylase determinations are needed for diagnostic studies. Lipase and trypsin values occasionally may add information in infants with suspected cystic fibrosis and in children with undiagnosed diarrheas and steatorrheas (10). Limitation of enzyme determinations to amylase tremendously simplifies the secretin test and obviates the collection of duodenal specimens in a cooled container such as an ice bucket.

Amylase determinations are done with ease using a modification of the Somogyi starch hydrolysis method as is currently used for blood amylase analyses (11). The concentration of protein in the duodenal drainage is not sufficient to interfere with the determination of the sugar formed from the reaction



Thus the protein precipitation step of the Somogyi method for blood is unnecessary. Otherwise, the blood amylase procedure in use may be employed for duodenal amylase by substituting a 1:50 or a 1:250 dilution of duodenal drainage for the undiluted blood serum. The amylase concentration expressed in units can be calculated from the equation (2)

$$\text{Amylase units} = KD \quad \text{Where } K = \frac{1}{30} \log \frac{7.5}{7.5 - a}$$

"a" representing the amount of maltose in mg. obtained in the reaction mixture

which has been incubated for 30 minutes at 37°C. With a photoelectric colorimeter for sugar analysis, a duodenal amylase determination should take no more than one hour.

Lipase concentrations are conveniently obtained either by studying the degradation of a natural fat, e.g. olive oil; an artificial one, e.g. tributyrin; or a completely synthetic one (2). The enzyme concentration may be calculated by titration of the fatty acid liberated or by studying the alteration in viscosity of the substrate medium (2).

Trypsin values can be obtained by incubation of the duodenal drainage with gelatine, a protein such as casein, or with ox hemoglobin. The Anson-Mirsky pepsin determination is easily modified for trypsin (12). The incubation period is short, 10 minutes at 37°C, the analysis a simple determination of liberated tyrosine by photoelectric colorimeter, and the procedure easily accomplished within 30 minutes.

The biliary pigment response to secretin (13-15) is studied by observing the bile pigment concentration of the individual duodenal specimens. This is accomplished by doing an icterus index colorimetrically on each sample. The specimens may be centrifuged and the sediment examined microscopically for crystals. The secretin test for biliary function must be considered an extension of the Lyon-Meltzer drainage. Whenever there is interest in gall bladder function,  $MgSO_4$  may be administered intraduodenally after the completion of the secretin test. Duodenal suction is discontinued for 10 minutes. Then upon resumption of drainage, "B" bile will be obtained in patients with gall bladder function.

The performance of a secretin test, thus, should require about 30 minutes for intubation, 40-80 minutes for drainage, and about 90 minutes for analysis, a total of about 3 hours which is not overlong in comparison to other modern diagnostic tests.

#### NORMAL RANGES FOR 30, 60, AND 80 MINUTE TESTS

The use of the secretin response in investigative or diagnostic problems requires the establishment of normal ranges derived statistically from the study of data of patients without evidence of pancreatic disease. Such ranges have been reported for other secretin preparations (1, 2, 16) but there is no data for the Lilly secretin. Theoretically there should be little difference between the effects of well standardized preparations derived from the same animal source (hog). However, experience has shown that some variation does occur with different secretins and different technique (2). The statistical ranges to be presented were derived from an analysis of the volume, bicarbonate and amylase responses in tests performed upon 123 subjects without evidence of pancreatic disease. This material is submitted not merely to serve as a control series for studies which will be performed in other laboratories but rather as a reference. It is strongly urged that any group using the secretin test perform at least 25 tests in normal patients. From these studies not only normal ranges may be established but also valuable experience with the technical problems of the procedure may be obtained.



TABLE I  
*Statistical Analysis of Secretin Volume Response Data of 123 Patients without  
 Pancreatic Disease*

	Total Volume Secretion, ml.			Total Volume Secretion, ml. kg.		
	30 min.	60 min.	80 min.	30 min.	60 min.	80 min.
Number of Cases (N).	123	123	123	123	123	123
Observed Range	54-220	91-270	117-392	1.0-2.8	1.6-4.8	2.0-6.2
Mean ( $\bar{x}$ ) $\pm \sigma_{\bar{x}}$	104.7 $\pm$ 2.1	164.7 $\pm$ 2.7	200.3 $\pm$ 3.3	1.73 $\pm$ 0.3	2.72 $\pm$ 0.5	3.22 $\pm$ 0.5
Standard Deviation ( $\sigma_x$ )	22.8	29.2	36.1	0.33	0.53	0.55
Coef. of Variation ( $V_c$ )	21.7%	18.3%	18.1%	19.1%	19.2%	17.0%
Calculated Range ( $\bar{x} \pm 2\sigma$ )	62-153	102-223	128-272	1.1-2.4	1.7-3.8	2.1-4.3

$$\text{Mean} = \bar{x} = \frac{\sum x}{N}$$

$$\text{Standard deviation} = \sigma_x = \sqrt{\frac{\sum x^2}{N} - \frac{(\sum x)^2}{N^2}}$$

$$\text{Standard deviation mean} = \sigma_{\bar{x}} = \frac{\sigma_x}{\sqrt{N}}$$

$$\text{Coef. of variation } V_c = \frac{\sigma_x}{\bar{x}} \times 100$$

$$\text{Calculated normal range} = \bar{x} \pm 2\sigma_x$$

A. *Volume Data.* The volume response secretion in total ml. and total ml. per kg. is given in Table I for 30, 60, and 80 minute collections. Judging from the coefficients of variation, satisfactory ranges can be obtained for all three periods. The rate of volume flow falls off rapidly after secretin from an average of 3.3 ml. per minute for the first 30 minutes, to 2.0 ml. per minute for the second 30 minutes and to 1.8 ml. per minute for the final 20 minutes of collection. Expressing the volume on a per kilogram basis may be done for convenience. It does slightly reduce the statistical scatter of the data.

B. *Bicarbonate Data.* The bicarbonate data for 30, 60, and 80 minute collection is given in Table II. If the maximum bicarbonate concentration is determined, the collection time makes little difference providing 10 minute samples are taken for at least 30 minutes so that a true maximum is obtained. There were only four instances in which differences were observed in the 30, 60, and 80 minute data. These differences were so small that they are not reflected in the statistical factors. For this reason the same range and data is presented for the three collection times.

The total bicarbonate secretion data show that the rate of bicarbonate secretion, like the rate of volume flow, falls off rapidly following secretin. During the first 30 minutes an average of 0.39 mEq. per minute is secreted, during the second 30 minutes the rate of bicarbonate secretion was 0.22 mEq. per minute, and finally during the last 20 minute collection the rate was 0.15 mEq. per minute. Judging from the coefficients of variation, ranges of comparative statistical scatter can be obtained for all three collection times. It is to be noted that the scatter in the bicarbonate data (maximum concentration and total bicarbonate

TABLE II

*Statistical Analysis of Secretion Bicarbonate Response Data of 123 Patients without Pancreatic Disease*

	Maximum Bicarbonate Concentration, mEq. L. 30 min.—60 min.—80 min.	Total Bicarbonate Secretion, mEq.		
		30 min.	60 min.	80 min.
Number of Cases (N).	123	123	123	123
Observed Ranges	88-137	6.8-16.0	13.2-23.7	15.9-32.6
Mean ( $\bar{x}$ ) $\pm$ $\sigma_{\bar{x}}$	107.7 $\pm$ 0.7	11.27 $\pm$ 0.10	17.81 $\pm$ 0.17	20.83 $\pm$ 0.18
Standard Deviation ( $\sigma_x$ )	8.3	1.13	1.84	2.01
Coefficient of Variation ( $V_c$ )	7.4%	10.0%	10.3%	9.7%
Calculated Range ( $\bar{x} \pm 2 \sigma_x$ )	91-125	9.0-13.6	14.1-21.5	16.8-24.9

secretion) is much less (coefficient of variation, 10 per cent) than that observed for the total volume secretion (coefficients of variation, 20 per cent) and, as will be subsequently demonstrated much less than that shown by the enzyme (amylase) secretion data. The bicarbonate response is the most characteristic and reliable attribute of pancreatic secretion following secretin (17). This is in accordance with Thomas' views of the significance of the secretin mechanism of pancreatic secretion, viz. maintenance of duodenal homeostasis through the neutralization of gastric acid by secreted bicarbonate (18).

C. *Amylase Data.* The total amylase secretion data for 30, 60, and 80 minute collections is given in Table III. The data is expressed in total unitage and in unitage per kilogram.

The rate of total amylase secretion unlike volume and bicarbonate secretion appears to be relatively unaffected by secretin. The total unit secretion per 30 minutes is of the same order of magnitude in the 30, 60, and 80 minute data with the exception that the average rate of secretion for the first 30 minutes, 16.0 units per minute is slightly greater than that for the second 30 minutes, 11.4 units per minute and that of the last 20 minutes, 11.6 units per minute. The slight initial increased yield in enzyme flow during the first 30 minutes is probably due to the washing out of preformed enzyme.

It is to be noted that the variability of the amylase data is much greater than that for volume and bicarbonate. With 80 minute collection, especially with data which has been expressed upon a per kilogram basis, the coefficient of variation, 22.0 per cent, is low enough to permit the derivation of a statistically significant normal range. The 60 minute data shows far greater variability and the normal range obtained is much wider so that only very great alterations in amylase secretion can be labelled as statistically abnormal. With 30 minute amylase values, the coefficient of variation is over 50 per cent. No satisfactory total amylase range can be established. The 30 minute amylase values can be viewed only qualitatively in the "all or none" sense. This lack of significance of enzyme data for short collection periods has been commented upon by Dornberger (5) and others (1).

Since there is no evidence for the existence of hypersecretion of the pancreas

TABLE III  
*Statistical Analysis of Secretin Amylase Response Data of 123 Patients without Pancreatic Disease*

	Total Amylase Secretion, units			Total Amylase Secretion, u. kg.		
	30 min.	60 min.	80 min.	30 min.	60 min.	80 min.
Number of Cases (N).....	123	123	123	123	123	123
Observed Ranges.....	145-1254	204-1621	439-1921	2.3-15.3	3.7-22.8	6.0-27.2
Mean ( $\bar{x} \pm \sigma_x$ ).....	480.7 $\pm$ 25.7	722.4 $\pm$ 24.9	1055 $\pm$ 25.0	6.9 $\pm$ 0.4	10.3 $\pm$ 0.3	14.9 $\pm$ 0.3
Standard Deviation ( $\sigma_x$ )...	282.6	274.3	275.3	3.6	3.7	3.3
Coefficient of Variation ( $V_c$ ).....	58.7%	38.1%	26.1%	52.6%	35.9%	22.0%
Calculated Range ( $\bar{x} \pm 2 \sigma_x$ ).....		173-1270	505-1605		2.9-17.4	8.3-21.5

(external secretion) as a clinical entity, the minimal values of the statistical ranges derived above can be accepted as the critical values in estimating normalcy of response to secretin. These critical values are summarized in Table IV.

#### INTERPRETATION OF TEST DATA

The pancreatic response to secretin can be affected by lesions which obstruct the flow of secreted juice or by pathologic processes which injure the secreting cells. Amongst the former are neoplasms which alter the response by virtue of the site and degree of pancreatic duct obstruction (19). Thus the characteristic secretin response in a patient with a pancreatic tumor is a decrease in volume flow. Whatever juice is able to pass the obstruction or by-pass it via the accessory duct may be qualitatively normal, e.g. of normal bicarbonate and enzyme concentration. Those tumors which do not obstruct a major pancreatic duct, viz. lesions of the tail of the pancreas, cannot be expected to alter the pancreatic response to secretin.

Inflammatory lesions of the pancreas injure the secreting cells and therefore alter the pancreatic secretion by affecting not only volume but also bicarbonate and enzyme secretion. There is good evidence of dissociation of response amongst these factors (2, 10, 17, 20). Whether this indicates a differential loss of function between the acinar and intralobular duct cells has been debated (21). It must be borne in mind that the external secretion of the pancreas following the onset of an attack of acute pancreatitis rapidly returns towards normal, so that abnormalities in the pancreatic secretion may not persist following clinical recovery from acute pancreatitis. In patients with chronic pancreatitis in which sufficient damage to the parenchyma has occurred to alter the secretin response, the defect in the secretin test is observed primarily in the bicarbonate data (17). Of course, extensive disseminated pathology of the secreting parenchyma, either inflammatory or neoplastic, may reduce all three factors, volume secretion, bicarbonate secretion, and amylase secretion.

The biliary pigment response describes the biliary flow and gives information as to the patency of the extrahepatic biliary tract and as to the presence or ab-

TABLE IV

*Critical Values (Lower Limit of Normal Statistical Ranges) of Secretin Response Data for Volume, Bicarbonate and Amylase Derived from a Study of Data from 123 Patients without Pancreatic Disease*

Collection Time, minutes	Total Volume, ml.	Total Volume, ml./kg.	HCO <sub>3</sub> Maximum Conc., mEq. L.	Total HCO <sub>3</sub> , mEq.	Total Amylase, units	Total Amylase, u./kg.
30	62	1.1	91	9.0		
60	102	1.7	91	14.1	173	2.9
80	128	2.1	91	16.8	505	8.3

sence of gall bladder function. Four fundamental types of response have been observed:

1. flow characteristic of a patent ductal system and normal gall bladder function—bile though initially present disappears from the duodenal drainage during the secretin test.

2. flow characteristic of lack of gall bladder function as in patients with cholecystic disease and patients following cholecystectomy—bile is present in good concentration throughout the secretin test.

3. flow indicative of complete biliary obstruction—bile is absent from the duodenal drainage during the test.

4. flow indicative of partial common duct obstruction—bile disappears from the duodenal drainage in a patient whose gall bladder has been previously removed.

The information obtained from the pancreatic response to secretin coupled with that from the biliary pigment response may be of considerable value in the elucidation of various disease syndromes, viz. obstructive jaundice, the post-cholecystectomy syndrome, the diarrheas, and the steatorrheas. In obstructive jaundice, precise localization of pathology is possible (16). In patients with the post-cholecystectomy syndrome, chronic pancreatitis and partial common duct obstruction can be diagnosed (22). Finally, the contribution of deficient external pancreatic secretion to the etiology of various digestive disorders such as sprue, ileitis, ulcerative colitis, may be evaluated with the secretin test.

#### SUMMARY

1. The precise technique of the secretin test is presented.
2. Normal ranges for the volume, bicarbonate, and amylase secretion have been derived statistically from the data of 123 patients without pancreatitis who were studied with secretin, Lilly.
3. The clinical application of the pancreatic and biliary pigment responses to secretin is commented upon.

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## INDEX TO VOLUME TWENTY-ONE

- A**DELMAN, Milton H., The anesthetic management of the cardiac patient with a note on induced hypotension, 355
- Adlersberg, D., et al., Plasma lipid partition of the normal and cholesterol-fed rabbit, 19
- Alkali-resistant hemoglobin in siblings with unusual blood pictures, (M. Lorber), 247
- Alumni award, David Beck, 163  
Richard Lewisohn, 162  
Bernard S. Oppenheimer, 163  
Bela Schick, 162
- Amyloidosis, systematized, associated with multiple myeloma, some unusual cutaneous, cardiac and gastrointestinal manifestations of, (J. K. Perloff), 195
- Anatomy, pathologic, in modern medicine, (P. Klemperer), 38
- Anesthetic management of the cardiac patient with a note on induced hypotension, (M. H. Adelman), 355
- Arrheno-blastoma, successful treatment of, (G. Felshin, B. Berglas), 209
- Arteriosclerosis, pathogenesis of, (P. Moschcowitz), 49
- Arthritis, rheumatoid, Problems in the management of, (S. Davison), 165
- Autonomic dysfunction, familial, (R. E. Moloshok, R. N. Reuben), 137
- B**AEHR, G., Profile of a surgeon, 337  
Beck, David, Alumni award, 163
- Benign tumor of the ureter, (G. D. Oppenheimer, L. Narins), 213
- Berglas, B., et al., Masculinizing tumor of the ovary: Successful treatment of an arrheno-blastoma, 209
- Bernstein, Solon S., Obituary, 1
- Biel, L., et al., A report on the use of the starch sponge cone in prostatectomy, 45
- Blum, L., Recent trends in the treatment of peripheral vascular diseases, 87
- Borken, N., et al., Elevations in temperature of joint, muscle and skin, following injection of prisco-line intra-arterially, 98
- Bornstein, M., et al., Pneumoencephalography with minimal withdrawal of cerebrospinal fluid, 299
- Bowel, infarction of, with occlusion of the mesenteric arteries and veins, (P. Kirschner), 307
- Braunwald, E., et al., The problem of chylothorax, 62
- with a note on induced hypotension, (M. H. Adelman) 355
- Cerebral cortex, electrical response of, to corticopetal impulses, (M. Ostow), 226
- Chemistry, clinical, modern developments in, (H. Sobotka), 142
- Chylothorax, the problem of, (E. Braunwald, J. Uhr), 62
- Colon, lipoma of, (B. S. Wolf, M. Melamed, M. T. Khilnani), 80
- Cutaneous, cardiac and gastrointestinal manifestations of systematized amyloidosis associated with multiple myeloma, (J. K. Perloff), 195
- Cytology, vaginal, the clinical status of, (L. Blum), 92
- D**AVISON, S., Problems in the management of rheumatoid arthritis, 165  
et al., Elevations in temperature of joint, muscle and skin, following injection of prisco-line intra-arterially, 98
- Drachman, S. R., et al., Plasma lipid partition of the normal and cholesterol-fed rabbit, 19
- Dreiling, E. A., The technique of the secretin test: normal ranges, 363  
et al., Pancreatitis, A review, 122, 176
- E**CZEMA, ocular; its classification and treatment, (F. H. Theodore), 255
- Electrical response of the cerebral cortex to corticopetal impulses: a comparison of peripheral and contralateral cortical stimulation, (M. Ostow), 226
- Encephalitis with a clinical picture of schizophrenia, (E. A. Weinstein, L. Linn, R. L. Kahn), 341
- F**AMILIAL autonomic dysfunction, (R. E. Moloshok, R. N. Reuben), 137
- Feldman, R. L., Chronic tubo-ovarian colonic fistula, 318
- Feitelberg, S., et al., Method for the determination of radioiodine levels in blood plasma, 296
- Felshin, C., et al., Masculinizing tumor of the ovary: Successful treatment of an arrheno-blastoma, 209
- Fistula, colonic, chronic, tubo-ovarian, (R. L. Feldman), 318
- Frishwasser, E. J., et al., A report on the use of the starch sponge cone in prostatectomy, 45
- G**AMMA globulin, the use of in infection refractory to antibiotics, (J. R. Harris, B. Schick), 148
- Gastrointestinal, cutaneous and cardiac manifestations of systematized amyloidosis associated with multiple myeloma, (J. K. Perloff), 195
- Genkins, G., et al., Studies in myasthenia gravis: cardiac and associated pathology, 218
- C**ARDIAC and associated pathology: studies in myasthenia gravis, (H. Mendelow, G. Jenkins), 218  
cutaneous and gastrointestinal manifestations of systematized amyloidosis associated with multiple myeloma, (J. K. Perloff), 195  
Cardiac patient, anesthetic management of,

- Globulin, acid precipitable, turbidity: A convenient guide to the status of serum alpha-2 plus beta globulins, (E. M. Greenspan), 279
- acid precipitable, turbidity, the effect of hepato-biliary diseases on, (E. M. Greenspan), 270
- Greenspan, E. M., The effect of hepato-biliary diseases on the serum acid precipitable globulin (APG) turbidity, 270
- The acid precipitable globulin (APG) turbidity: A convenient guide to the status of serum alpha-2 plus beta globulins, 279
- Grishman, A., et al., Interatrial conduction defects associated with supraventricular tachycardia in individuals without organic heart disease, 26
- Guttmacher, A. F., Therapeutic abortion, 111
- HARRIS, J. R.**, et al., The use of gamma globulin in infection refractory to antibiotics, 148
- Hemoglobin, high alkali-resistant, in siblings with unusual blood pictures (M. Lorber), 247
- Hepato-biliary diseases, effect of, on the serum acid precipitable globulin (APG) turbidity, (E. M. Greenspan), 270
- Hypertension, essential, numerical evaluation of ocular signs of, (H. Minsky), 29
- Hypoglycemia, spontaneous, (P. Kornfeld), 321
- Hypertension induced, a note on, for the anesthetic management of the cardiac patient, (M. H. Adelman), 355
- INFARCTION** of the bowel with occlusion of the mesenteric arteries and veins, (P. Kirschner), 307
- Interatrial conduction defects associated with supraventricular tachycardia in individuals without organic heart disease, (M. B. Walters, A. Grishman), 26
- JOINT**, muscle and skin, elevations in temperature of following injection of priscoline intra-arterially, (S. Davison, N. Borken, M. Wolf), 98
- KAHN, R. L.**, et al., Encephalitis with a clinical picture of schizophrenia, 341
- Khilnani, M. T., et al., Lipoma of the colon, 80
- Kirschner, P. A., Occlusion of the mesenteric arteries and veins with infarction of the bowel, 307
- Klemperer, P., Pathologic anatomy in modern medicine, 38
- Kornfeld, P., Spontaneous hypoglycemia, 321
- LAPID, L. S.**, The clinical status of vaginal cytology, 92
- Lewisohn, Richard, Alumni award, 162
- Lichtenstein, R., et al., Pneumoencephalography with minimal withdrawal of cerebrospinal fluid, 299
- Linn, L., et al., Encephalitis with a clinical picture of schizophrenia, 341
- Lipid, plasma, partition of the normal and cholesterol-fed rabbit, (C. I. Wang, L. E. Schaefer, S. R. Drachman, D. Adlersberg), 19
- Lipoma of the colon, (B. S. Wolf, M. Melamed, M. T. Khilnani), 80
- Lorber, M., High alkali-resistant hemoglobin in siblings with unusual blood pictures, 247
- MASCULINIZING** tumor of the ovary: Successful treatment of an arrhenoblastoma, (G. Felshin, B. Berglas), 209
- Melamed, M., et al., Lipoma of the colon, 80
- Mendelow, H., et al., Studies in myasthenia gravis: cardiac and associated pathology, 218
- Mesenteric arteries and veins, occlusion of, with infarction of the bowel, (P. Kirschner), 307
- Minsky, H., Numerical evaluation of ocular signs of essential hypertension, 29
- Minsky, Henry, obituary, 107
- Moloshok, R. E., et al., Familial autonomic disfunction, 137
- Moschcowitz, E., Pathogenesis of arteriosclerosis, 49
- Moseley, J. E., et al., Cervical thymus gland, 289
- Muscle, joint and skin, Elevations in temperature of, following injection of priscoline intra-arterially, (S. Davison, N. Borken, M. Wolf), 98
- Myasthenia gravis, studies in: cardiac and associated pathology, (H. Mendelow, G. Jenkins), 218
- Myeloma, multiple, some unusual cutaneous, cardiac and gastrointestinal manifestations of systematized amyloidosis associated with, (J. K. Perloff), 195
- NARINS, L.**, et al., Benign tumor of the ureter, 213
- New aspects of pathogenesis of experimental poliomyelitis, (G. Schwartzman), 3
- Newburger, R. A., et al., Method for the determination of radioiodine levels in blood plasma, 296
- Numerical evaluation of ocular signs of essential hypertension, (H. Minsky), 29
- OBERNDORF, Clarence P.**, obituary, 103
- Obituary, Solon S. Bernstein, 1
- Henry Minsky, 107
- Clarence P. Oberndorf, 103
- Occlusion of the mesenteric arteries and veins with infarction of the bowel, (P. Kirschner), 307
- Ocular eczema; its classification and treatment, (F. H. Theodore), 255
- signs of essential hypertension, numerical evaluation of, (H. Minsky), 29

- Oppenheimer, Bernard S., Alumni award, 163
- Oppenheimer, G. D., et al., A report on the use of the starch sponge cone in prostatectomy, 45
- Benign tumor of the ureter, 213
- Ostow, M., Electrical response of the cerebral cortex to corticopetal impulses; a comparison of peripheral and contralateral stimulation, 226
- Ovary, masculinizing tumor of: Successful treatment of an arrheno-blastoma, (G. Felshin, B. Berglas), 209
- PANCREATITIS**; A review, (D. A. Dreiling, A. Richman), 122, 176
- Pathogenesis of arteriosclerosis, (E. Moschowitz), 49
- Pathologic anatomy in modern medicine, (P. Klemperer), 38
- Peripheral vascular diseases, recent trends in the treatment of, (L. Blum), 87
- Perloff, J. K., Some unusual cutaneous cardiac and gastrointestinal manifestations of systematized amyloidosis associated with multiple myeloma, 195
- Plasma lipid partition of the normal and cholesterol-fed rabbit, (C. I. Wang, L. E. Schaefer, S. R. Drachman, D. Adlersberg), 19
- Pneumoencephalography with minimal withdrawal of cerebrospinal fluid, (P. Slosberg, M. Bornstein, R. Lichtenstein), 299
- Poliomyelitis, experimental, New aspects of pathogenesis, (G. Schwartzman), 3
- Priscoline, injection of intra-arterially, Elevations in temperature of joint, muscle and skin, following, (S. Davison, N. Borken, M. Wolf), 98
- Profile of a surgeon, (G. Bachr), 337
- Prostatectomy, A report on the use of the starch sponge cone in, (G. D. Oppenheimer, L. Biel, E. J. Frishwasser), 45
- RADIOIODINE** levels in blood plasma, method for the determination of, (S. Silver, R. A. Newburger, S. B. Yohalem, S. Feitelberg), 296
- Reuben, R. N., et al., Familial autonomic dysfunction, 137
- Rheumatoid arthritis, problems in the management of, (S. Davison), 165
- Richman, A., et al., Pancreatitis: A review, 122, 176
- SCHAEFER, L. E.**, et al., Plasma lipid partition of the normal and cholesterol-fed rabbit, 19
- Schick, B., et al., The use of gamma globulin in infection refractory to antibiotics, 148
- Schick, Bela, Alumni award, 162
- Schizophrenia, encephalitis with a clinical picture of, (E. A. Weinstein, L. Linn, R. L. Kahn), 341
- Secretin tests, the technique of; normal ranges, (E. A. Dreiling), 363
- Shwartzman, G., New aspects of pathogenesis of experimental poliomyelitis, 3
- Silver, S., et al., Method for the determination of radioiodine levels in blood plasma, 296
- Skin, joint and muscle, Elevations in temperature of, following injection of priscoline intra-arterially, (S. Davison, N. Borken, M. Wolf), 98
- Slosberg, P., et al., Pneumoencephalography with minimal withdrawal of cerebrospinal fluid, 299
- Sobotka, H., Modern developments in clinical chemistry, 142
- Som, M., et al., Cervical thymus gland, 289
- Starch sponge cone in prostatectomy, a report on the use of, (G. D. Oppenheimer, L. Biel, E. J. Frishwasser), 45
- Supraventricular tachycardia in individuals without organic heart disease, interatrial conduction defects associated with, (M. B. Walters, A. Grishman), 26
- THEODORE, F. H.**, Ocular eczema; its classification and treatment, 255
- Therapeutic abortion, (A. F. Guttmacher), 111
- Thymus gland, cervical, (J. E. Moseley, M. Som), 289
- Treatment of peripheral vascular diseases, recent trends in, (L. Blum), 87
- Tubo-ovarian colonic fistula, chronic, (R. L. Feldman), 318
- UHR, J.**, et al., The problem of chylothorax, 62
- Ureter, benign tumor of, (G. D. Oppenheimer, L. Narius), 213
- VAGINAL** cytology, the clinical status of, (L. S. Lapid), 92
- WALTERS, M. B.**, et al., Interatrial conduction defects associated with supraventricular tachycardia in individuals without organic heart disease, 26
- Wang, C. I., et al., Plasma lipid partition of the normal and cholesterol-fed rabbit, 19
- Weinstein, E. A., et al., Encephalitis with a clinical picture of schizophrenia, 341
- Wolf, B. S., et al., Lipoma of the colon, 80
- Wolf, M., et al., Elevations in temperature of joint, muscle and skin, following injection of priscoline intra-arterially, 98
- YOHALEM, S. B.**, et al., Method for the determination of radioiodine levels in blood plasma, 296



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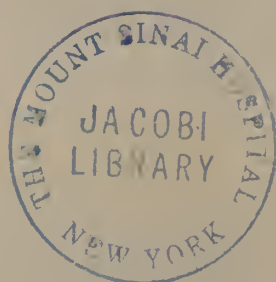
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